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THE CHEMICAL BEHAVIOR OF THE ORGANOALKALI COMPOUNDS [1]

AVERY A. MORTON

Research Laboratory of Organic Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

CONTENTS

I. INTRODUCTION

This review presents a general theory of the behavior of organoalkali reagents,—a theory based on (a) the existence and reactions of an ion-pair in a non-dissociating solvent, and (b) the presence of a dominant metal ion which has a powerful attraction for electrons. The reactions of the ion-pair are linked with the behavior of all salts in general, and the effect of the metal ion is classed with that of electron-attracting substituents, such as the nitro, ammonium, and other common groups attached to aromatic systems.

Although the formal classification of material is that given in the table of contents, the general understanding of this paper, particularly of the latter half,

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will be made easier by the statement of a simple, yet reasonable, sequence of opinion and argument which has formed the basis for much of the author's reflection on the subject. This series of guiding principles is:

(1) Organosodium compounds are salts, an opinion now generally accepted.

(2) A great disparity in strength between the two components of the salt exists, and the reactivity usually increases as the disparity increases.

(3) This lack of balance results in a display of residual force which emanates from the stronger component, because its affinity is unsatisfied.

(4) For a reagent which consists of two components, adjacent to each other but of great inequality in strength, it is the part of common sense to express the reactions as deriving a major impulse from the stronger component, unless unquestioned reasons can be advanced for supporting a contrary view.

(5) An exterior force, which is capable of separating the salt into its two parts, may make it possible for each portion to act independently, to an extent depending on the degree of separation and on the potency of single as compared with joint action of the ions.

It will be made clear that one of the principal facts which justify the above sequence is that the conditions under which the organoalkali reagents are prepared and used are, in general, those in which neither of the ions of the salt can move from the vicinity of the other. Hence, while as salts the organoalkali compounds show properties characteristic of salts in general, the differences in strength cause the cation to play a prominent part in all reactions, even those in which the action appears to be localized in the anion.

The above sequence, in general, runs parallel to the table of contents, but the space allotted to the first point, the matter of the salt-like nature of the organoalkali compounds, comprises nearly a third of the paper. The discussion of acidity and salt formation covers a wide range, and extends even to the more common type of the carboxylic acids. The remaining points in the sequence are argumentative in nature, designed to assist in interpreting some of the reactions of organoalkali compounds which now appear to be of an unusual or peculiar nature but which, by this discussion, are brought into line with other well-known reactions or principles in organic chemistry.

The general aim in this review is not to offer a complete bibliography in the field, though the list is of necessity fairly generous, but to present a rational treatment of the chemistry of these compounds, in order to establish a sound basis for interpreting known facts and predicting new ones.

II. THE SALT-LIKE NATURE OF ORGANOALKALI REAGENTS

The salt-like character of organoalkali compounds[2] forms the basis for the discussion presented in this paper. The correctness of this viewpoint is now generally accepted. The electronic formula requires it, conductance measurements support it, and physical properties accord with it.

[2] The commonly accepted definition of organoalkali compounds—namely, that they are compounds in which carbon is attached to an alkali metal—is used in this paper.

A. The electronic formula

The electronic formula requires that the valence between carbon and sodium be ionic (11), because an octet of electrons about the sodium ion is complete and the additional electron of the sodium atom forms part of the system of eight that surrounds the carbon atom. The octets about sodium and carbon contain no electrons shared with each other; hence the valence must be an electrostatic one.

$$\overset{\displaystyle \text{H}}{\underset{\displaystyle \text{H}}{\text{R} \colon \! \overset{\cdot\cdot}{\underset{\cdot\cdot}{\text{C}}} \colon}} \, \overset{+}{\text{Na}}$$
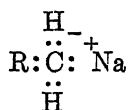
B. Conductance of salts

Numerous conductance measurements support this idea: ethylsodium in diethylzinc (61); benzylsodium in ether (105); triphenylmethylsodium in ether (106, 32), pyridine (137), and liquid ammonia (78); and the Grignard reagent in ether (77, 19). Conductance in these solutions is low. Dielectric constants of 4.7 for ether, 12.5 for pyridine, and 22 for liquid ammonia, as compared with 81.1 for water, insure that the electrostatic attraction between the ions remains high, particularly so in ether, one of the common solvents. Dissociation of the ions is accordingly much lower than is found in aqueous solutions of the more common salts.

Occasionally a salt fails to conduct the current. Phenylsodium (61), for example, does not conduct the current in dimethylzinc, although phenyllithium does. An explanation for this abnormality is not clear. Fortunately other properties are such that the salt-like nature of this reagent can be accepted.

C. Physical properties

Physical properties of the organoalkali compounds, such as insolubility in organic solvents, decomposition without melting when heated, and non-volatility, accord, in general, with those of the common salts. All organoalkali compounds do not share these properties equally. The variations led Ziegler (133) to divide these compounds into three groups.

(1) *Colorless salts*, which are insoluble in organic solvents, are heteropolar in the solid state, and are conductors of an electric current when dissolved in dimethylzinc. Alkyl- and aryl-sodium and potassium compounds are examples of this class.

(2) *More or less intensely colored compounds*, often very soluble in organic solvents, which conduct an electric current. The metal is attached to a carbon atom, which is attached also to a double bond or a benzene ring. Benzylsodium, benzyllithium, and phenylisopropylpotassium are examples of this class.

(3) *Colorless compounds* which are soluble in organic solvents and which distill or sublime. The physical properties appear analogous to those of the alkylzinc and alkylcadmium compounds of Group II of the Periodic Table. They are

non-electrolytes and conduct poorly in zinc alkyls. The alkyllithium compounds are examples.

The first two classes include compounds which are distinctly salt-like; the last includes those of doubtful salt character. The fact that organolithium compounds dissolve in organic solvents and melt without decomposition need not perhaps be surprising in view of the fact that inorganic lithium salts, such as the bromide or iodide, are soluble in ether and that the inorganic lithium compounds, in general, melt appreciably lower than the corresponding sodium or potassium ones. This review, however, makes no distinction between organo-alkali compounds of different classes nor seeks any explanation for the absence of some expected properties in one class, because, in a large number of reactions, such a separation serves no useful purpose. Indeed, one aspect of this presentation is the view that the electrostatic bond in the salts has much in common with the covalent bond in the distinctly organic compounds. For the remainder of this paper, all organoalkali compounds are regarded as salts without further regard to fine distinctions which, in our present incomplete state of knowledge, affect the chemical properties slightly, if at all.

The system of naming which designates organoalkali compounds as derivatives of the metal, e.g., ethylsodium, originated before their salt-like character was fully recognized. There is no special name reserved for this class of salts. A few attempts have been made to emphasize the relation to other salts by names, such as sodium methide (12) or sodium ethide, analogous to sodium amide. In the case of amylsodium this system might lead to some confusion with the amine salt, unless the term "sodium pentide" were used. Although the present convention of naming is inconsistent with the well-defined salt-like character of some of these compounds, the use of expressions such as amylsodium, phenyllithium, or phenylisopropylpotassium, that suggest covalence, may after all serve to emphasize the opinion that the distinction is in many cases a physical one and that the chemical properties of these unique salts, under the condition in which they are usable, frequently parallel the properties found in compounds whose bonds are unquestionably of the convalent type.
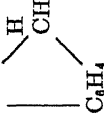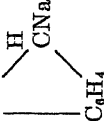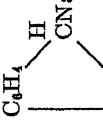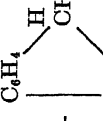
III. THE ACIDITY OF THE ACID COMPONENT OF THE SALT

If organoalkali compounds are salts, the hydrocarbon portion must be derived in some manner from an acid, and the acidity of this acid must be of an extremely low order. The common expression "pseudo acid" reflects, in part, the general opinion of a lack of true acidic properties in the hydrocarbon from which the salt is, theoretically, derived but often cannot be obtained by direct action with the metal. Within the ranges covered by these compounds, however, the relative acidities are as meaningful as they are with the stronger carboxylic acids. The comparisons will, indeed, be shown to be very striking.

A. The method of measuring the acidity

The general method of measuring the acid strength in this series is one of replacement of a weak acid by a stronger one. Table 1 shows a graded series

TABLE 1

Graded replacement series connecting organometallic salts with the common salts

Increasing strength of acids →

REACTIVE SALT	+	ACID	(ACIDITY SCALE) →	LESS REACTIVE SALT	PRODUCTS + WEAKER ACID	
$C_5H_{11}Na$	+	C_6H_5H	10^{-89} ⇌	C_6H_5Na	+	$C_5H_{11}H$
C_6H_5Na	+	$C_6H_5CH_2H$	10^{-38} ⇌	$C_6H_5CH_2Na$	+	$C_6H_5CH_2H$
$C_6H_5CH_2Na$	+	$(C_6H_5)_3CH$	10^{-33} ⇌	$(C_6H_5)_3CNa$	+	$C_6H_5CH_2H$
$(C_6H_5)_3CNa$	+	$C_6H_4\!\!<\!\!{}^{H}_{}CH\!\!>\!\!C_6H_4$	10^{-25} ⇌	$C_6H_4\!\!<\!\!{}^{H}_{}CNa\!\!>\!\!C_6H_4$	+	$(C_6H_5)_3CH$
$C_6H_4\!\!<\!\!{}^{H}_{}CNa\!\!>\!\!C_6H_4$	+	C_2H_5OH	10^{-18} ⇌	C_2H_5ONa	+	$C_6H_4\!\!<\!\!{}^{H}_{}CH\!\!>\!\!C_6H_4$
C_2H_5ONa	+	HOH	10^{-14} ⇌	$HONa$	+	C_2H_5OH
$HONa$	+	C_6H_5OH	10^{-10} ⇌	C_6H_5ONa	+	HOH
C_6H_5ONa	+	CH_3COOH	10^{-5} ⇌	CH_3COONa	+	C_6H_5OH
CH_3COONa	+	HCl	⇌	$NaCl$	+	CH_3COOH

← Increasing reactivity of salts

which illustrates the process and, at the same time, links the salt-like character of the organosodium compounds to the better-known salts of the stronger acids.

The most authoritative study of this point and, indeed, the only one which assigns numerical values to the degree of acidity, is that made by Conant and Wheland (15) and later extended by McEwen (81). These investigators measured, under equilibrium conditions, the direction of change in several ways: a colorimetric one in the case of colored salts, a carbonation process followed by isolation of the respective acids, a spectroscopic method in which etioporphyrin I was used as an indicator, and a polarimetric one with some optically active compounds. They assigned approximate values of strength on the basis of the usual equation for comparing acids

$$pK_1 - pK_2 = \log \frac{[R_1^-]}{[R_1H]} - \log \frac{[R_2^-]}{[R_2H]}$$

pK_1 and pK_2 are the respective acid strengths, R_1^- and R_2^- are the concentrations of the respective ions, and R_1H and R_2H are the concentrations of the corresponding acids. The assumptions are that the metallic salts are equally dissociated and that the pseudo acids are not dissociated. The concentrations of the ions of the salt can therefore be substituted for those of the acids. According to this equation the reaction will proceed 90 per cent to completion if the acids differ by 2 pK units when the quantities used are equal. Since a fivefold excess was used in the colorimetric measurements, a difference of 0.4 pK unit could exist. In the series of McEwen (81), the known value of 16 for methanol serves as a reference standard from which approximate values of pK are assigned to the other acids. The results of these studies are listed in table 2, in the order of decreasing strength and with the acidic hydrogen shown in heavy type.

The valuable series given in table 2 can be supplemented by information from replacement reactions in which the tendency to metalate, the comparative yields, and the ease of reaction have been noted. Such measurements are subject to special factors such as the insolubility of one or both of the organoalkali compounds present or the cation used (see Section IV A), and hence are not as suitable for determining the relative acidity as are the experiments made under equilibrium conditions. Nevertheless a surprising degree of unanimity is often found in the results of different investigators, many of whom had no thought of determining relative reactivities. Several examples of this method of judging the order of acid strength can be given.

Schorigin's (107) observation that ethylsodium reacts with benzene, toluene, and diphenylmethane rates ethane as a much weaker acid than any of the other three compounds. Amylsodium (85) attacks benzene, and phenylsodium, in turn, attacks toluene. Potassium amide (129), in liquid ammonia, does not substitute in toluene but does in diphenylmethane. Moreover, the series in table 2 shows that triphenylmethane is a stronger acid than diphenylmethane, from which the inference can be drawn that toluene, in which just one phenyl group is present, is less acidic than diphenylmethane. The reasonable deduction for the order of acid strength is: pentane or ethane < benzene < toluene < ammonia < diphenylmethane.

TABLE 2

Order of acidity as listed by Conant and Wheland and by McEwen

ACID	pK	ACID	pK
CH₃OH	16	C_6H_5NH (with H above) ⎫⎪ ⎬ p—CH₃C₆H₄NH (with H above) ⎪ p—CH₃OC₆H₄NH (with H above) ⎭	27

Left column (ACID / pK):

- CH₃OH . . . . — 16
- C₄H₄NH[a] . . . . — 16.5
- (CH₃)₂C(H)OH ⎫
  C₂H₅OH ⎬ . . . . — 18
  C₆H₅CH₂OH ⎭
- (CH₃)₃COH ⎫
  C₁₀H₁₉OH[b] ⎪
  C₆H₅C(O)CH₂H ⎬ . . . . — 19
  (C₆H₅)₃COH ⎭
- [C₆H₄ / C₆H₅[c] — C — C₆H₄ / H] ⎫
  ⎪
  C₆H₄—CH=CH—C—H[d] ⎬ . . . . — 21
  (with H above) ⎪
  [C₆H₄ / C₁₀H₇(α) — C — C₆H₄ / H] ⎪
  C₆H₅C≡CH ⎭
- (C₆H₅)₂NH . . . . — 23
- [C₆H₄ \\ H / CH / C₆H₄] . . . . — 25

Right column (ACID / pK):

- C₆H₅NH (H above) ⎫
  p—CH₃C₆H₄NH (H above) ⎬ . . . . — 27
  p—CH₃OC₆H₄NH (H above) ⎭
- [O—C₆H₄ / C₆H₅ — C — C₆H₄ / H] ⎫
  ⎬ . . . . — 29
  [O—C₆H₄ / H[e] — C — C₆H₄ / H] ⎭
- (C₆H₅)₂ =CH . . . . — 31
  C₆H₄C₆H₄
- (C₆H₅)₃CH . . . . — 33
- (C₆H₅)₂ =CH . . . . — 34
  (α)C₁₀H₇
- (C₆H₅)₂CH (H above) . . . . — 35
- (C₆H₅)₂C=CH—CH (H₂ above) . . . . — 36
- C₆H₅CH(CH₃)₂ . . . . — 37
- C₂H₅H . . . . — [40][f]

[a] Pyrrole.
[b] Menthol.
[c] 9-Phenylfluorene.
[d] Indene.
[e] Xanthene.
[f] Estimated value.

A similar series can be arranged from data of Gilman and coworkers. Butyl-, phenyl-, α-naphthyl-, and p-methoxyphenyl-lithiums give 55, 12, 7.6, and 0 per cent yields, respectively, of the lithium salt of dibenzothiophene (31). Benzylsodium (39) metalates dibenzofuran. Neither dibenzofuranylsodium (39) nor triphenylmethylsodium (25) will attack dibenzothiophene. The orders, as judged from the data, are (1) butane < benzene < naphthalene < dibenzothiophene < anisole (para position) and (2) toluene < dibenzothiophene < dibenzofuran or triphenylmethane. The probable acidity of dibenzothiophene is in the neighborhood of 10^{-33} to 10^{-36}.

Other measurements of the same type have been made. Ziegler and coworkers (136) showed that phenylisopropylpotassium introduces a metal in 1,1-diphenylpropenyl, $(C_6H_5)_2C\!=\!CHCH_3$, and that phenyllithium attacks diethyl-amine (134). Gilman (25) showed that diphenyl ether is metalated by butyl-lithium but not by triphenylmethylsodium. By similar studies (27) triphenyl-methane is rated weaker than furan, which in turn is weaker than phenyl-acetylene, rated 10^{-21} (table 2).

It is clear from the foregoing that the interchange of acids in a salt is very common and is virtually the only method now available for measuring the comparative acidities of these weak acids. When such processes can be carried out under equilibrium conditions a reliable opinion can be formed. When carried out in the usual manner the results, while not as accurate, nevertheless offer a satisfactory basis for establishing the probable order of acidity.

B. The effect of substituents on the acidity and the relative order of acid strengths

The evidence that phenyl groups increase the acidity of these hydrocarbo acids is clearly marked. In addition to the increase in the series methane, toluene, diphenylmethane, and triphenylmethane, 9-phenylfluorene is more acidic than fluorene (table 2). Presumably 9-phenylxanthene is more acidic than xanthene, although the method of measurement did not permit a fine distinction. The conclusion appears justified that attachment of a phenyl group to a carbon atom bearing an acidic hydrogen raises the acid strength.

Alkylation of any kind appears to lower the acidity. The comparative strengths of the alkanes may be judged from the fact that amylsodium attacks benzene or toluene more readily than does butylsodium, which in turn acts more readily than propylsodium (96). In fact, toluene can be used as a solvent in the preparation of propylsodium from propyl chloride and the metal. Increasing chain length is accordingly associated with greater reactivity of the salt and, therefore, with less acidity of the acid.

tert-Butyl-, isopropyl-, butyl-, and methyl-lithiums form the lithium salt of dibenzofuran (39) with decreasing ease. tert-Butyllithium attacks toluene more readily than does butyllithium (39, 40). These results indicate that alkyl chain branching, as well as chain lengthening, decreases the acid strength.

Confirmatory observations of the decrease in acidity with alkylation come from the greater difficulty experienced in metalation, once alkyl groups are intro-

duced (unless, of course, the alkyl group introduced is itself metalated as in the case of a change from benzene to toluene). For example, o-, m-, or p-xylene is metalated by amylsodium (88) with more difficulty than is toluene; and the ortho isomer is attacked with more difficulty than the other two, probably because of the proximity of the two methyl groups. Butyl- or amyl-benzene is metalated (96) with more difficulty than is toluene. Two methyl groups, introduced into the alkyl portion of toluene (that is, to form isopropylbenzene), so reduce the acidity of the hydrogen on the side chain that the para position of the ring becomes a preferred point for salt formation (89). Furthermore, ethylsodium metalates the side chain with the least number of alkyl groups in p-cymene, i.e., the methyl in place of the isopropyl group (107).

These evidences of reduced acidity on alkylation have an interesting parallel in the observations of Ingold and coworkers (58, 72) that the decomposition of tetrasubstituted ammonium salts proceeds less readily when alkyl branching or alkyl chain lengthening occurs on the β-carbon atom. He appropriately attributes the effect to a reduction in the "incipient acidity" of the hydrogen atom on the β-carbon.

All these results confirm the opinion that the tertiary hydrogens in paraffin hydrocarbons are less acidic than the secondary hydrogens and that these in turn are less acidic than primary hydrogen atoms.

The effect of oxygen atoms on the acidity cannot be predicted at the present time with much certainty. As far as ethereal oxygen is concerned, the acidity appears to be raised. For example, xanthene can be regarded as diphenylmethane with an oxygen bridge. According to table 2, the first is a stronger acid than the second, $K_A = 10^{-29}$ and 10^{-35}, respectively. The increase may, however, be more the effect of a union of two rings than an oxygen ether influence, since fluorene is a markedly stronger acid than diphenylmethane.

Furan is metalated by triphenylmethylsodium but not by sodium phenylacetylide (27); therefore its acidity may be between 10^{-21} and 10^{-33}. Dibenzofuran (48) is weaker than dibenzothiophene. Diphenyl ether (25) is metalated by ethylsodium or butyllithium but not by triphenylmethylsodium, and is therefore probably weaker than 10^{-33}. Anisole is metalated by butyllithium, butylsodium, phenylsodium (25), and amylsodium (86). One difficulty in attempting to evaluate the influence of ethereal oxygen is that any effect of oxygen on the acidity may also be influenced by the facility with which organoalkali reagents cleave the ether (Section IV C). The question of the influence of other types of oxygen, such as esters or ketones, will be presented as a part of the next section (III C).

A general over-all order for hydrocarbons and some ring systems may be arranged as follows:

Alkane (tertiary)		Diphenylmethane	10^{-35}
Alkane (secondary)		Triphenylmethane	10^{-33}
Alkane (primary)	$< 10^{-37}$	Xanthene	10^{-29}
Methane		Aniline	10^{-27}
Benzene		Fluorene	10^{-25}
Toluene	near 10^{-37}	Phenylacetylene	10^{-21}

Introduction of phenyl groups into any of these systems will, in general, increase the acidity. Introduction of alkyl groups will decrease the acidity. Oxygen, in the form of ether, possibly strengthens the acidity, other factors being equal.

C. The relationship to other acids and salts

By and large, substituents have the same qualitative effect on acidity whether they are introduced into hydrocarbons, amines, alcohols, or carboxylic acids. The similar character of this effect is very clear in the case of phenyl groups (see table 3). The progressive introduction of the phenyl nucleus in methane has already been shown to cause a decided increase in acid strength. Its introduction into ammonia likewise increases the acidity (81), and conversely decreases the basicity (110). Sodium amide, as predicted from such basicity studies, will metalate aniline (116). The known difference in acidity between phenol (110)

TABLE 3

Effect of introducing phenyl groups into acids

NUMBER OF PHENYL SUBSTITUENTS	pK				
	CH_4	NH_3		H_2O	CH_3COOH
	K_A	K_A	K_B	K_A	K_A
None.........	?		1.85×10^{-5}	1.0×10^{-14}	1.75×10^{-5}
One...	$<10^{-35}$	10^{-27}	5.0×10^{-10}	1.0×10^{-10}	4.88×10^{-5}
Two... ...	10^{-35}	10^{-23}	*		11.5×10^{-5}
Three........	10^{-33}				

* Too weak to measure in water (52).

and water shows that the phenyl group exerts a similar effect when the acidic hydrogen is attached to oxygen instead of to nitrogen or carbon. The acidity of acetic acid shows a similar trend when phenyl is introduced.

There are many other instances of increase in acidity caused by introducing phenyl groups. Phenylhydrazine ($K_B = 1.6 \times 10^{-9}$) is more acidic than hydrazine ($K_B = 3 \times 10^{-6}$) and is metalated by sodium amide in liquid ammonia to give $C_6H_5N(Na)NH_2$ (3). Phenylacetylene (25) is stronger than acetylene, judged by metalation studies. Two phenyl groups substituted in propene, $(C_6H_5)_2C=CHCH_3$, raise the acidity so as to permit substitution by phenylisopropylpotassium (133). Thiophenol is a stronger acid than hydrogen sulfide. It is clear from all this evidence that the introduction of phenyl into the system H_nXH, where X is either a bi-, tri-, or tetra-valent atom, or into any system where the acidic hydrogen is in a position conjugated with X, as in the above-mentioned propene compound, will invariably increase the acidity of the hydrogen. The introduction of a phenyl group into any position of a molecule does not, however, necessarily raise the acidity of carboxylic acids, since benzoic acid (110) is weaker ($K = 6.3 \times 10^{-5}$) than formic acid ($K = 1.76 \times 10^{-4}$) and β-phenylpropionic acid is not appreciably different from propionic acid (18). In a similar way 1,1,1-triphenylethane (129), $(C_6H_5)_3CCH_3$, is not acidic enough

to be affected by potassium amide in liquid ammonia. The activating influence is realized when the phenyl group is attached directly or through a vinyl system to the atom which holds the acidic hydrogen or acid-functioning group (128). When it is otherwise situated, the effect need not be the same.

The vinyl group, like the phenyl, confers marked acidity on acids. The fact that the ionization constant (110) of vinylacetic acid is a little less (3.8×10^{-5}) than that of phenylacetic acid (5.4×10^{-5}) suggests that substitution in the hydrocarbo acids would be a little more difficult when the activation is by a vinyl rather than a phenyl group. In agreement with this expectation, propene is not metalated as readily as is toluene. When two vinyl groups are present and are connected with each other, the activation is appreciable. Cyclopentadiene (53) is metalated by such a mild reagent as ethylmagnesium bromide; pyrrole, also, has a hydrogen which is acidic enough to be detected by the Grignard reagent (132) in pyridine solution at 85°C. The marked activity of the hydrogen atoms in fluorene in the reaction with a Grignard reagent (52, 132) is readily explained on the basis that a divinyl system, activated by two benz groups, is present.

A similar parallelism, in an opposite direction, can be shown to result from the introduction of alkyl groups. The weakening of the acidity in the nitrogen series is seen by the increase of the basicity (inverse of the acidity) (20) and the decrease of the ionization potential (114) of ammonia as alkyl groups are introduced. Similarly, the acidity becomes weaker as water (10^{-14}), methanol (10^{-16}), and ethanol (10^{-18}) are compared (81). The series methanol, isopropyl alcohol, and *tert*-butyl alcohol likewise shows decreasing acidity (table 2). The same alkyl influence is found in changing from acetic to trimethylacetic acid (18).

Exceptions to this general rule of decreased acidity with increased alkylation are few in number. The ionization constants of carboxylic acids show some irregularity with chain lengthening, which Dippy (18) ascribes to chelation of the hydrogen on the γ-carbon atom with the carbonyl oxygen. Heptylacetylene (25) is stronger, rather than weaker, than acetylene, judged by metalations with the lithium salt. Sodium isobutyrate (85) is metalated more readily by amylsodium than is sodium caproate, a circumstance that may be related to the difficulty of adequate contact in a mixture in which both reagents are insoluble.

The remarkable similarity in the effects of phenyl or alkyl groups in hydrocarbo, ammono, or carboxylic acids suggests that similar parallel effects will be encountered for carbethoxy or other groups. That is to say, since a carbethoxy group will raise the acidity of a carboxylic acid, it should also raise the acidity of a hydrocarbo acid. Such reasoning leads to the opinion that the hydrogen in ethyl acetate or ethyl malonate is acidic. Practical results indicate that the acidity of ethyl acetate is of a relatively high order, comparable with that of ethyl alcohol, for the reaction of sodium ethoxide with ethyl acetate is an equilibrium process. This view is advanced by Chelintzev (14) and by Hauser (59, 60) as preferable to the older view of Claisen of an addition product between the ester and the alcoholate:

$$NaOC_2H_5 + CH_3COOC_2H_5 \rightleftarrows HOC_2H_5 + NaCH_2COOC_2H_5$$
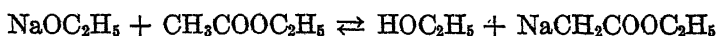
This opinion is in accord, also, with the fact that as an alkylated ester is used, i.e., as ethyl propionate and higher members are treated with sodium ethoxide, the acidity of the ester is weaker and the equilibrium lies further toward the left. Hence the reaction to the right needs to be forced by volatilization of the ethyl alcohol formed in the process (11). Moreover, with esters which are more difficult to convert to the sodium salt, the use of the more reactive triphenyl-methylsodium (K_A of $(C_2H_5)_3CH$ is 10^{-33}) has been shown by Hauser (59) to be preferable to sodium ethoxide (K_A of C_2H_5OH is 10^{-18}). Even in this case alkylation, superimposed on the carbethoxy effect, reduces the acidity, for the metalation of the ester should and does, in some cases at least, proceed with more difficulty as the chain is lengthened. For example, triphenylmethylsodium metalates ethyl diethylacetate, $(C_2H_5)_2CHCOOC_2H_5$, in 30 min. and ethyl isobutyrate, $(CH_3)_2CHCOOC_2H_5$, in 5 min. (59). According to the principles which have been presented earlier, the first compound would be a weaker acid than the second and, therefore, harder to metalate.

The carbonyl group, also, has a pronounced effect on acidity. Sodium amide (estimated value of K_A for NH_3 is 10^{-30}) metalates (57) acetophenone ($K_A = 10^{-19}$) and like compounds. The salt produced is one in which the anion exists in two resonance forms, judged by the fact that a subsequent reaction with ethyl chloroformate sometimes produces a carbon derivative and at other times an oxygen derivative. Introduction of alkyl groups into the ketone, as seen below, favors the oxygen form; and this fact would be expected, since alkyl groups reduce the acidity of the hydrogen on the carbon atom to which the groups are directly attached.

$$C_6H_5 \underset{O}{\overset{\|}{C}} CH_3 \xrightarrow[\text{(2) ClCOOC}_2\text{H}_5]{\text{(1) NaNH}_2} C_6H_5 \underset{O}{\overset{\|}{C}} CH_2 COOC_2H_5$$

$$C_6H_5 \underset{O}{\overset{\|}{C}} CH_2 CH_3 \xrightarrow[\text{(2) ClCOOC}_2\text{H}_5]{\text{(1) NaNH}_2} C_6H_5 \underset{OCOOC_2H_5}{\overset{|}{C}}\!\!=\!\!CHCH_3 \; + \; C_6H_5 C\!\!=\!\!C \overset{CH_3}{\underset{\substack{COOC_2H_5 \\ OCOOC_2H_5}}{\diagdown}}$$

$$C_6H_5 \underset{O}{\overset{\|}{C}} CH(CH_3)_2 \xrightarrow[\text{(2) ClCOOC}_2\text{H}_5]{\text{(1) NaNH}_2} C_6H_5 \underset{OCOOC_2H_5}{\overset{|}{C}}\!\!=\!\!C(CH_3)_2$$

$$(CH_3)_3 \underset{O}{\overset{\|}{C}} CCH(CH_3)_2 \xrightarrow[\text{(2) ClCOOC}_2\text{H}_5]{\text{(1) NaNH}_2} (CH_3)_3 C \underset{OCOOC_2H_5}{\overset{|}{C}}\!\!=\!\!C(CH_3)_2 \; +$$

$$(CH_3)_3 C \underset{O}{\overset{\|}{C}} C\!\!-\!\!\underset{COOC_2H_5}{\overset{|}{C}}(CH_3)_2$$
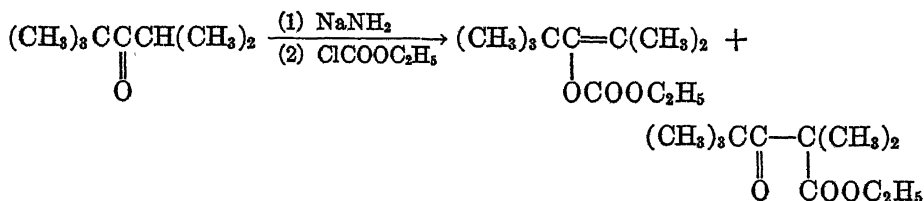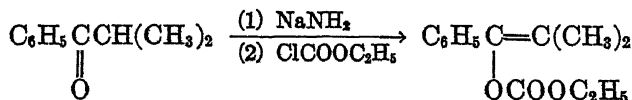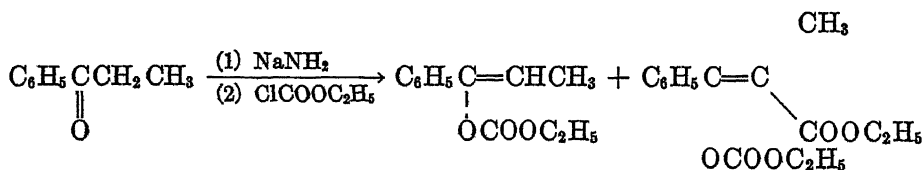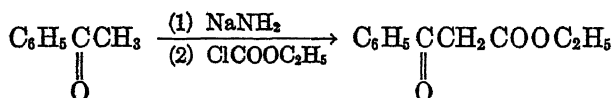
This problem of metalation of compounds which contain carbethoxy or car-bonyl groups is complicated by the fact that the reagent can add as well as sub-

stitute, a mixture of effects which will be met later in this paper (Section IV B). In order to emphasize the relationship between the hydrocarbon and other types of acids, the influence of such groups, and for that matter of nitrile and nitro groups, will be expressed as a labilizing of the acidic hydrogen, and the structure of the ionized form will be regarded as a resonance hybrid between the carbon atom and the negative pole of the activating group.

A number of interesting summaries can now be made. Table 4 lists (a) some of the common acids, including hydrocarbon, alcoholic, and carboxylic; (b) the group which influences the acidity of each acid; (c) the salt commonly used

TABLE 4

Acids, activating group, and reagent used for replacement of hydrogen

ACID	GROUP ACTIVATING THE ACID	SALT COMMONLY REQUIRED FOR SUBSTITUTION	ATTACHMENT OF THE METAL ION IN THE PRODUCT
Alkanes.............	Alkyl groups	None so far known	
Benzene or toluene....	Benzene ring	Alkylsodium compounds	Metal attached solely to carbon
Acetophenone........	Carbonyl group	Sodium amide	Metal attached to a resonance hybrid between carbon and oxygen
Ethyl acetate........	Carbethoxy group	Triphenylmethyl-sodium	
Ethyl acetoacetate...	One carbonyl and one carbethoxy group	Sodium ethoxide	
Acetonitrile...........	Cyano group	Lithium amides, sodium ethoxide	Metal attached to a resonance hybrid between carbon and nitrogen
Alcohols..............	Alkoxy radical	Sodium acetylide, Grignard reagents. Equilibrium with salts of hydroxides	Metal attached solely to one oxygen
Carboxylic acids.. ..	Carboxyl radical	Alkaline hydroxides	Metal attached to resonance hybrid of two oxygen atoms

for metalation; and (d) the position in the anion where the metal ion is attached. The table is arranged in order of increasing acidity of the acid which reacts with the metal salt. The acid strength increases as the activating group changes from phenyl to carbonyl or carbethoxy and cyano, and increases further as the hydrogen shifts from a position on carbon to one on oxygen, and still further to one on a carboxyl group. Correspondingly, the salt required to metalate the acid need be less and less reactive, and the product becomes more and more stable.

Table 5 presents the acidity relationship from another angle. A limited number only of acids are indicated, but the relative positions of acids activated by similar groups are shown by dotted lines. It is clear that there is a gradual drop

in acid strength as the hydrogen is attached to carbon, nitrogen, oxygen, or carboxyl. It is also true that in all series, the acidity increases as the possibility of resonance increases, as judged by the effect of such unsaturated systems

TABLE 5

Approximate relative positions of corresponding acids in different series
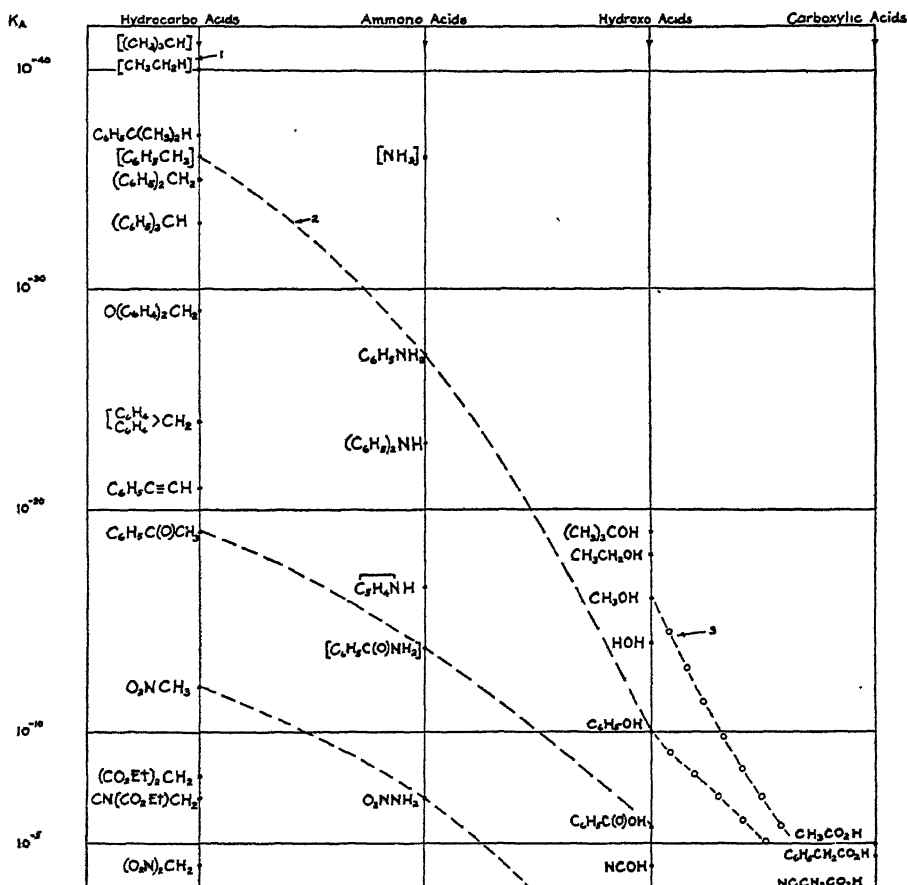
Positions of compounds enclosed in brackets are estimated. Ammonia is placed above diphenylamine because of the observation of Wooster (128), that the hydrogen in a benzohydryl type compound was replaced by metal in reaction with potassium amide. If the position of ammonia is correct, the values for methane, ethane, and trimethylmethane may be considerably less than indicated.

Dotted lines connect the corresponding acids in different series.

Dashes and circles, rather than dotted lines, connect the hydroxo acids to members of the carboxylic acid series, because the latter do not represent a truly different series, but merely hydroxo acids, activated by an adjacent carbonyl group.

as carbethoxy, carbonyl, nitrile, and nitro groups. Dinitromethane, for example, is acidic enough to be measured by conductance (110).

The relationship can also be presented by the electronic picture below, which

emphasizes the positions of carbon, nitrogen, oxygen, and chlorine in the Periodic Table:

IV	V	VI	VII

$$\underset{\substack{\text{xx} \\ \text{R}}}{\overset{\text{R} \\ \text{xx}}{\text{R \ddot{\text{x}} C}}} : H \qquad \overset{\text{R} \\ \text{xx}}{\text{R \ddot{\text{x}} N}} \left.:\right\} H \qquad \text{R \ddot{\text{x}} O} \left.:\right\} H \qquad \text{Cl} \left.:\right\} H$$

$$\underrightarrow{\text{Decreased tendency to hold a proton}}$$
Increased tendency for stable octet without covalence

The ionization increases progressively as the number of electrons to which the proton can be attached increases; or, expressed in another way, the chance of a proton being separated becomes greater as the anion becomes able to maintain a stable octet without the assistance of covalence with the proton and other radicals. This chance is at a minimum for carbon and at a maximum for chlorine.

In the carbon, nitrogen, and oxygen series of acids, the acids become stronger as the system is fortified by resonance. For example, the alcoholic acid is strengthened by another oxygen atom, as in the carboxylic acids, and the latter is still further strengthened by a nitrile group. Similarly, the hydrocarbon acids are strengthened by nitrile or nitro groups.

The description of these relationships is greatly simplified. There are unquestionably some factors, peculiar to each series, which would prevent an exactly parallel effect. At the present moment, however, the scheme serves to show the broad principles involved and to indicate that, within the region where the hydrocarbon acids react, the acidity relationships, and hence the salt-like character of many reactions of the organometallic compounds can be as real as those which prevail among the better-known acids and salts.

IV. THE COMMON REACTIONS

A. Substitution

One of the common reactions of the organoalkali compounds is substitution. This reaction, as far as replacement of hydrogen is concerned, has already been discussed at some length in the section dealing with the measurement of the acidities of the acids, and will be mentioned frequently in other portions of this paper.

The potency of an organometallic reagent in such a reaction might reasonably be regarded as related to the difference in strength between the anion and cation, for if acids vary in strength and bases vary in strength, the various combinations of acids and bases (known as salts) must also vary according as the respective strengths are compensated; the differences will be made manifest by different reactivities of the salts, leading toward greater compensation of the forces involved. The cause of this difference is not known. The electrical charge is theoretically neutralized, for whether the salt is amylpotassium, amylsodium, sodium amide, or sodium chloride, the cation and the anion have charges repre-

sented by the loss and the gain of one electron, respectively. The disposition of the electrons in each ion, however, must have a great influence. Although it is possible to speculate on the relation of mass, volume, electron orbits, and the like to the comparative activities of lithium, sodium, potassium, and other cations, and to ponder on the influence of groups on the stability of the system of eight electrons in the anion when one pair is without the fixing influence of a covalence, this review is concerned primarily with the manifestations, rather than the cause, of variable activity.

It has already been made clear that the activity increases as the acid to which the anion is related becomes weaker, the cation at the same time being constant. It is equally true that the reactivity increases as the cation changes. The Grignard reagent attacks anisole (13) only at high temperature; butyllithium metalates it near room temperature. Butyllithium in turn will introduce one metal atom only into furan and has a limited action (15 per cent yield) on benzene (39); amylsodium will introduce two sodium atoms into furan (91), one sodium atom into benzene at around 25°C., and two sodium atoms into benzene (88) at 55–60°C. Ethyllithium, ethylsodium, and ethylpotassium attack dibenzofuran with increasing ease (46). The last two reagents cause dimetalation. The comparatively weak salt, ethylmagnesium bromide, reacts with toluene (64) only under special conditions, such as in hot toluene in the presence of p-isopropylbenzyl chloride, to give the disubstituted ethane, $(CH_3)_2CHC_6H_4\text{-}CH_2CH_2C_6H_5$. Alkyllithium compounds, however, metalate toluene (42) readily; amylsodium does so with great rapidity. Amylpotassium (87), but not amylsodium, will metalate 1-pentene easily.

These changes in reactivity accord with the view that the salt becomes more active as the difference in strength between cation and anion increases. The order for the strength of anions, as outlined in the previous section, might not be altered by a change in the cation, but the possibility of metalation when the two pseudo acids involved are near each other in acidity appears to be improved as the cation becomes stronger. This fact, undoubtedly, is important in any attempt to arrange an order of acidity for hydrocarbon acids on the basis of metalation experiments under non-equilibrium conditions, since a failure to metalate with a given salt may merely mean that the cation lacks sufficient strength to bridge the resistance toward a reaction which could otherwise take place.

B. Addition

At first thought the process of addition might be expected to be a very easy one. The fact that halogens add instantaneously to olefins, but substitute slowly in hydrocarbons, has contributed to the tradition that addition reactions are invariably preferred and that, if substitution does take place in a compound where double bonds are present, an addition process may have been its precursor. In spite of the facility with which addition to unsaturated systems occurs, organometallic reagents do not appear to add invariably to olefins, and there are reasons why, in certain instances, they might not be expected to add very readily. The

problem of addition is, in fact, complicated by the strong tendency toward substitution.

The simplest case that can be considered is the possibility of addition to an olefin, such as ethylene or a substituted ethylene. The products would be a long-chain or a branched-chain alkylmetal compound as indicated below:

$$RNa + H_2C=CH_2 \longrightarrow RCH_2-CH_2Na$$

$$RNa + R'CH=CHR'' \longrightarrow \begin{matrix} R & & H \\ \diagdown & & \diagup & + \\ & CH-C- & Na \\ \diagup & & \diagdown \\ R' & & R'' \end{matrix}$$

Reactive salts + Olefins $\longrightarrow$ More reactive salts
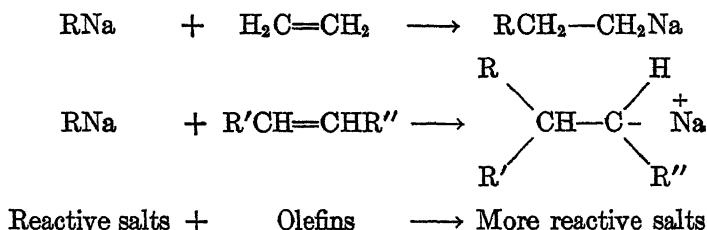
According to the principles discussed in a previous section, alkyl branching and alkyl-chain lengthening will reduce the acidity of the pseudo acid. Hence such addition will produce a salt more active than the reagent employed. This fact need not of course prevent the reaction, since, if the two acids in question are near enough in strength, an observable equilibrium might theoretically exist; and, because the carbon–carbon bond in the product is not labile, the process would be an irreversible one and would proceed to completion. If, however, substitution were possible at some position in the olefin—and the vinyl group will activate a hydrogen for replacement—the product would be a less reactive salt than the reagent. Therefore, unless the velocity of substitution is extremely slow compared to that of addition (admittedly a very important provision), or unless some other factor, such as insolubility, intervenes, substitution rather than addition would be the rule.

Experiment confirms the above deductions concerning addition reactions to *simple* olefins. 2-Phenylisopropylpotassium does not react with ethylene (133). The more reactive amylpotassium (87) reacts with 1-pentene, but the process is one of substitution, not of addition.

$$C_2H_5CH_2CH=CH_2 + C_5H_{11}K \rightarrow C_2H_5CHKCH=CH_2 + C_5H_{12}$$
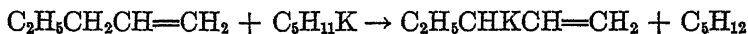
The chances of addition become more favorable when one of the carbon atoms of the olefin has a phenyl or aromatic system attached. Such a group, as mentioned before, increases the acidity of acids; and the product of addition would have a better chance of being a salt of less reactivity than the reagent. In spite of this assistance the tendency to add is by no means dominant. Table 6 shows the results obtained by Ziegler (133) and coworkers in the reaction of phenylisopropylpotassium with a number of olefins. It is apparent that addition will take place in every instance where there is only one phenyl group attached to carbon, except in one compound where two methyl groups are connected vinylogously to the activating ring; and, incidentally, that compound is also one in which a maximum amount of branching would have been present had addition occurred. Addition takes place also when the fluorene group is present.

The margin between addition or substitution, however, must be close, because the presence of two phenyl groups on the carbon atom in question causes substitution to be favored in every instance, even though the activating influence has to be transported through a vinyl group in order to make substitution possible. The presence of two phenyl groups on one carbon atom may retard but does not prevent an addition reaction, because unsymmetrical diphenylethylene, in which no very acidic hydrogen is present, adds the potassium reagent readily. It is clear, therefore, that in these examples substitution is preferred to addition.

When the activating group is a nitrile, carbonyl, or carboalkoxy group, the condition is different from that present in the reaction with olefins, because the

TABLE 6

Reaction of phenylisopropylpotassium with various unsaturated hydrocarbons

ADDITION REACTIONS	SUBSTITUTION REACTIONS*
$C_6H_5CH=CH_2$	$C_6H_5CH=C(CH_3)_2$
$(C_6H_5)_2C=CH_2$	$(C_6H_5)_2C=CHCH_3$
C_6H_5 $\diagdown$ $\quad C=CH_2$ $\diagup$ CH_3	$(C_6H_5)_2C=C(CH_3)_2$
$C_6H_5CH=CHCH_3$	$(C_6H_5)_2C=CHCH_2CH_3$
C_6H_4 $\diagdown$ $\quad C=CHCH_3$ $\diagup$ C_6H_4	$(C_6H_5)_2C=CHCH_2C_6H_5$

* The hydrogen replaced is shown in heavy type.

activating group is also the one to which addition occurs. On the one hand the probability of substitution is enhanced because the acidity promoted by a nitrile or carbonyl group is greater than that by a phenyl group. (The ionization constants (110) of cyanoacetic, glyoxylic, and phenylacetic acids are 3.7×10^{-3}, 4.7×10^{-4}, and 4.88×10^{-5}, respectively.) On the other hand, the addition process may overcome this advantage by the higher velocity with which addition to an unsaturated, and comparatively strongly polar, system may occur.

The very reactive salts, that is, the salts of extremely weak acids as represented by some organosodium, organolithium, and Grignard reagents, invariably add rather than substitute. The reactions are too common to list.

The less reactive salts, such as sodium amide, sodium alkoxides, and triphenylmethylsodium, will sometimes add, but they very frequently substitute, or at

least undergo a process the net result of which is equivalent to substitution. For example, addition of sodium amide to a nitrile (135), as in the equation below, produces a salt of an amidine, but reaction of lithium amide or lithium diethyl-

$$(CH_3)_2 CHCN + NaNH_2 \rightarrow (CH_3)_2 CH-\overset{\overset{\displaystyle NH_2}{|}}{C}=N-Na$$
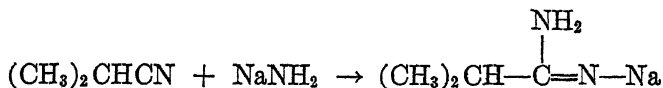
amide with the same compound results in substitution.

$$(CH_3)_2 CHC\equiv N \xrightarrow[\text{LiN}(C_2H_5)_2]{\text{LiNH}_2 \text{ or}} (CH_3)_2 C(Li)C\equiv N$$
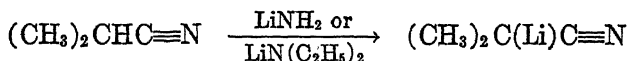
The mechanics of the substitution process are not known with sureness. A plausible explanation, frequently offered, is that addition takes place first, followed by elimination, so that the result is equivalent to substitution. This opinion is supported by the isolation of addition products in certain reactions. Potassium amide forms an intermediate with ethyl diphenylacetate (113); when heated, this intermediate liberates ammonia to form a potassium salt in which the metal is presumably attached to the resonance form of the ion.

$$KNH_2 + (C_6H_5)_2 CH\overset{\overset{\displaystyle O}{\|}}{C}OC_2H_5 \longrightarrow (C_6H_5)_2\overset{\overset{\displaystyle H}{|}}{C}-\overset{\overset{\displaystyle NH_2}{|}}{C}\overset{OK}{\underset{OC_2H_5}{<}}$$

$$\xrightarrow{-NH_3} [(C_6H_5)_2 C=\overset{\overset{\displaystyle O-}{|}}{C}OC_2H_5]^- \overset{+}{K}$$
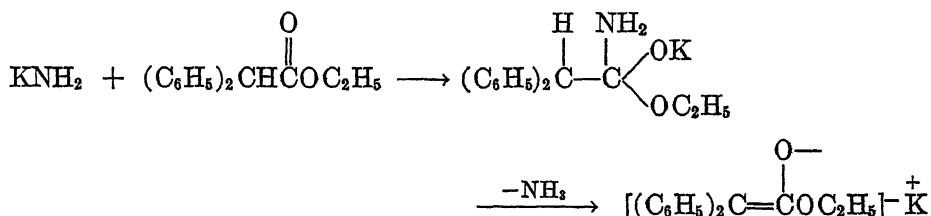
Sodium methoxide, also, forms an addition compound with ethyl benzoate (119). Adickes (1), however, failed to find evidence that such compounds were present with reagents used in preparations leading to compounds of the ethyl acetoacetate type.

In the present state of knowledge it is impossible to distinguish between a direct substitution and an indirect process by an addition mechanism when the final product contains a metal in place of hydrogen. Suitable pen and paper pictures can be constructed easily for either possibility.

Whatever the governing factor, substitution occurs readily with the less reactive reagents, and numerous processes rely upon a sequence of substitution followed by addition. For instance, the preparation of cyclic compounds from dinitriles by use of alkaline reagents shows both steps (see below). For making five- and six-membered rings, Thorpe (115) used sodium ethylate; for large rings, Ziegler (134) used lithium diethylamide.

Thorpe:

$$\begin{matrix} CH_2 CH_2 CN \\ | \\ CH_2 CH_2 CN \end{matrix} \quad NaOC_2H_5 \quad \begin{matrix} CH_2 CHC\equiv N \\ \diagdown Na \\ | \\ CH_2 CH_2 C\equiv N \end{matrix} \longrightarrow \begin{matrix} CH_2 CHC\equiv N \\ | \diagdown \\ \quad C=NNa \\ | \diagup \\ CH_2 CH_2 \end{matrix}$$

Ziegler:

$$\underset{(CH_2)_n}{\overset{CH_2 C\equiv N}{\diagdown \atop C\equiv N}} \quad \xrightarrow{\text{LiN}(C_2H_5)_2} \quad \underset{(CH_2)_n}{\overset{CHC\equiv N}{\diagup \atop \diagdown \atop C\equiv N}} \overset{|}{\text{Li}} \quad \longrightarrow \quad \underset{(CH_2)_n}{\overset{CHC\equiv N}{\diagup \atop \diagdown \atop C=NLi}}$$
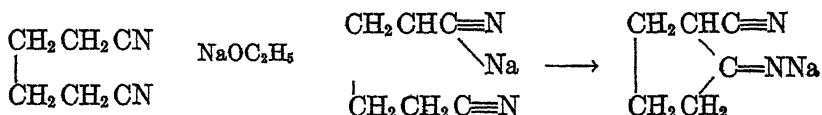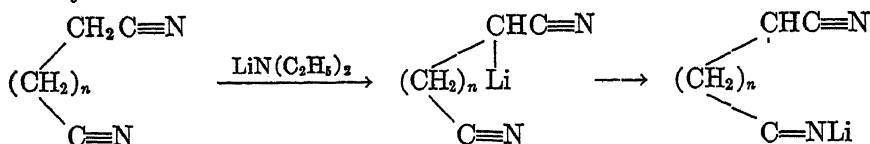
Similar ring formation occurs when the activating group is carbonyl (56).

$$\underset{CH_2 CH_2 C(O)C_6H_5}{\overset{CH_2 CH_2 C(O)C_6H_5}{|}} \quad \xrightarrow{\text{NaNH}_2} \quad \underset{CH_2 CH_2 \overset{O}{\overset{\parallel}{C}}C_6H_5}{\overset{CH_2 CHC(O)C_6H_5}{\overset{|}{} \text{Na}}} \quad \longrightarrow$$

$$\underset{H_2CH_2 \qquad C_6H_5}{\overset{CH_2 CHC(O)C_6H_5}{\diagdown \atop \underset{\diagup \diagdown}{CONa}}}$$
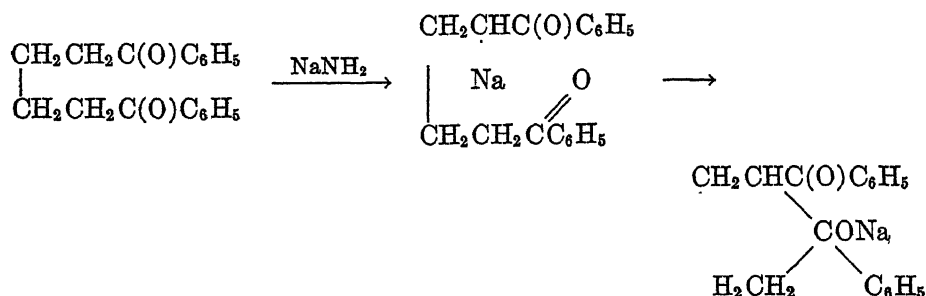
The well-known formation of ethyl acetoacetate has been interpreted (2, 14, 59, 60) as one of initial substitution in an equilibrium process, followed by addition. The alcohol formed in the first step can be removed by distillation (11) or by metallic sodium. When sodium alcoholate is the condensing agent, the first phase is not readily isolable because the alcohol produced is so acidic that an equilibrium exists. When triphenylmethylsodium (66) is used with dialkyl-substituted acids, the triphenylmethane is so weakly acidic, or the intermediate substitution product is so stable, that the reaction proceeds to the completion of the formation of substitution product in place of the self-condensation. The reagent which will induce a proper sequence of substitution and addition varies (109) with the substance being condensed. Sodium amide is not effective with ethyl acetate, whereas sodium alkoxide is. Sodium or potassium amide or iso-propylmagnesium bromide induce the condensation in ethyl phenylacetate or in *tert*-butyl acetate.

When addition takes place, the velocity appears proportional to the strength of the cation as long as the anion remains constant. The times required for completion of the reaction of phenylacetylides (49) with benzonitrile were found

$$C_6H_5C\equiv CM^3 \;+\; C_6H_5C\equiv N \;\longrightarrow\; \underset{\overset{|}{C\equiv CC_6H_5}}{C_6H_5C=NM}$$
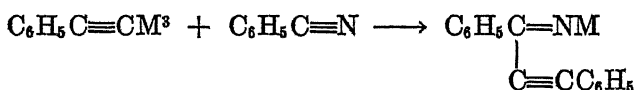
to be 2.9, 3.9, 4.4, 6.8, 60 and 86 hr., respectively, for the cesium, rubidium, potassium, sodium, lithium, and magnesium bromide salts.

The effect of a variation in the strength of the anion cannot be foretold with certainty, for two factors are at work: one the increased reactivity of the reagent salt as salts of weaker pseudo acids are employed, and the other the decreased strength of acid in the product salt caused by branching. In other words,

[3] M = a metal ion.

the anions in the reagents and in the product do not compete by interchange of a proton and an alkali cation, but unite in an irreversible process. The result is that the order found in the replacement studies is not always followed in the addition processes. For example, Ziegler (133) and coworkers noted that the reactions of ethyl-, propyl-, and butyl-lithiums with unsymmetrical diphenyl-ethylene at 50°C. were as 1.5 to 3.4 to 2.8, respectively; Gilman, Moore, and Baine (39) found that the percentage of addition to the same compound after 8 hr. in benzene with sec-butyl, isobutyl-, and butyl-lithium was 82, 13, and 12, respectively. These results are approximately in the order of greater reactivity as rated by the replacement series (Section III B) (although Ziegler's results showed a maximum value for propyllithium). On the other hand, the addition of the Grignard reagent to benzonitrile (42) showed roughly the opposite trend of less reactivity with more reactive salts, tert-butyl, sec-butyl-, butyl-, ethyl-, and phenyl-magnesium bromides requiring 25.5, 11.65, 4.57, 0.85, and 0.31 hr., respectively, for completion of the addition process. These orders are the inverse of that based on reactivity in replacement reactions. The variations are not the result of using benzonitrile in place of diphenylethylene, because similar irregularities can be found in each type of compound. Amyllithium added less readily than butyllithium to as-diphenylethylene, contrary to expectation; and the time required for addition to benzonitrile decreased in the series phenyl-, p-tolyl-, and mesityl-magnesium bromides from 0.31 to 0.10 to 0.01 hr., respectively, in agreement with the order of expected increase in reactivity. In general, the processes of addition do not furnish as reliable an index of reactivity as do those of substitution where, under certain conditions at least, equilibrium conditions exist and where the changes involve only a replaceable hydrogen in the pseudo acid, not a complete change by fusion of the anion with the pseudo acid.

C. Cleavage

It is characteristic of salts that they will cleave organic compounds wherever a more stable salt will form and the reagent has sufficient reactivity. Ethers are accordingly cleaved by some organometallic reagents, the products being metallic alkoxides or phenoxides. Amines are cleaved with more difficulty, for the metallic amide formed is in general a more reactive salt than is the alkoxide. The carbon–carbon bond is broken only when the bond is greatly activated by carbonyl and carboalkoxy groups. For example, ethyl acetoacetate is cleaved by such a comparatively mild reagent as sodium ethoxide, one of the products being the less reactive acetate.

Ordinary ether can be cleaved easily. Ethylsodium (107) reacts with it to form sodium ethoxide, ethane, and ethylene. Amylsodium cleaves ether so readily that it cannot be used as a solvent in reactions of that organoalkali reagent. Sec- and tert-alkyllithiums (30) react with ethyl ether rather rapidly. In contrast to the behavior of these reactive salts, methyllithium, which is, according to Section III, a very much weaker salt than the sec-, tert-, and n-alkyllithium reagents, can be kept in refluxing ether for 11 days without any action

taking place. The weaker Grignard reagents, also, can be kept in ether for indefinite periods.

Anisole (111) and phenetole (54), probably because of their high boiling points as well as the activation imparted by a phenyl nucleus, are cleaved at high temperature by methyl- and ethyl-magnesium iodides. Benzyl ethyl ether (112) reacts with methylmagnesium iodide to form ethylbenzene.

Ethylene oxide represents a still more reactive type of ether which is cleaved readily by Grignard reagents. It can be cleaved also by the moderately active ethyl sodioisobutyrate (67), $(CH_3)_2C(Na)C(O)C_2H_5$.

Amines should be cleaved also, but with more difficulty than the ethers. When methylmagnesium iodide and dimethylaniline (65) interact together at 215°C. and the mixture is carbonated, a major product is p-dimethylaminophenylbenzoic acid, $(CH_3)_2NC_6H_4C_6H_4COOH$. One dimethylamino group has obviously been separated by cleavage. The steps in this process might be formulated as follows:

$$CH_3I + Mg \rightarrow CH_3MgI$$

$$CH_3MgI + C_6H_5N(CH_3)_2 \rightarrow CH_4 + -C_6H_4- + (CH_3)_2NMgI$$

$$(CH_3)_2NMgI + C_6H_5N(CH_3)_2 \rightarrow (CH_3)_2NC_6H_4MgI + (CH_3)_2NH$$

$$(CH_3)_2NC_6H_4MgI + -C_6H_4- \rightarrow (CH_3)_2NC_6H_4C_6H_4MgI$$
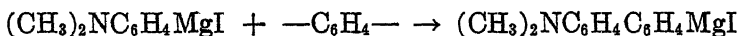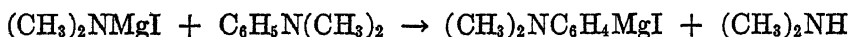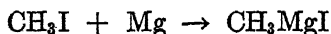
Other miscellaneous cleavage reactions occur. Diphenylmercury, for example, is cleaved by butyllithium (25) with formation of phenyllithium. Phenyl selenide (25) is cleaved readily by butyl ether under conditions in which phenyl sulfide is partially cleaved and partially metalated, and diphenyl ether is not cleaved at all but is metalated. Formals (117) are cleaved by the Grignard reagent. Organolead and other related compounds are cleaved by lithium reagents (40).

D. Dehydrogenation

Phenyllithium converts 1,4-dihydrodibenzofuran (26) and 1,4-dihydrodibenzothiophene (31) to dibenzofuran and dibenzothiophene according to the equation
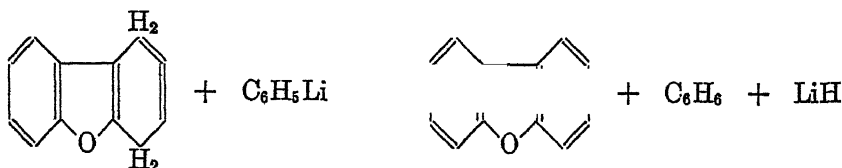
The reaction is not a general one for all hydroaromatic systems. The process is probably one of substitution, followed by elimination of lithium hydride, somewhat after the manner in which addition reactions, followed by elimination of an alkali hydride, occur (see Section VI C). The tendency for restoration of the conjugated cyclic structure plays a prominent rôle in such cases.

V. RESIDUAL POLARITY

In agreement with the hypotheses set forth at the beginning of this paper, a salt derived from a base and an acid of unequal strengths will necessarily have a degree of reactivity related to the inequalities involved, and the stronger of the two ions will have an activity commensurate with its uncompensated strength. This unbalanced effect, since it emanates from the cation, must be of a positive nature and will, therefore, attract and disturb electrons in other bodies in the immediate vicinity, preferably in the anion to which it is attached by an electrostatic force, but also possibly in other substances with which it happens to be in contact. The result will be that the cation, without itself participating directly in a reaction, will nevertheless affect the reaction of the anion or other body. To consider otherwise is to state that an extremely strong polar force will, for no good reason at all, cease to act like a positive pole.

Such residual polarity can be shown with advantage in orientation studies. Three cases exist. In the first the expected ortho–para-orienting effect is completely set aside by the metal ion and the substituting group is caused to enter the meta position or another ring. In the second, the ortho–para-directing influence is largely or entirely preserved but substitution is made more difficult. In the third, but not decisive case, the conventional meta orientation caused by a carboxyl or carbonyl group is altered and ortho–para orientation results.

A. Meta-directing influence of alkali-metal cation

The phenyl and benzyl ions, shown below, might be expected to show an ortho–para-directive influence because the electrons no longer held by a covalence

would be free to resonate with those in the ring and thus to increase the electron density in the aromatic nucleus. The results are quite contrary to such expectation. Metalation of phenylsodium and of benzylsodium takes place exclusively[4] in the meta position. The products obtained (88) by the action of amylsodium at 55–60°C. on these two salts are m-phenylenedisodium, m-Na$_2$C$_6$H$_4$, and m-homophenylenedisodium, m-NaC$_6$H$_4$CH$_2$Na.

So also in the case of the α- or β-naphthyl ions, the products expected from the anion acting alone would be the result of substitution, ortho or para to the α-

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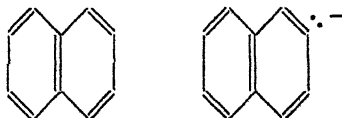
[4] This statement is true only if the stirring is adequate to secure thorough mixing of the reagents, both of which are insoluble. If the stirring is comparatively poor, a small amount of para substitution accompanies the meta substitution (85).

or β-position, respectively, because the electron density in the ring would be raised. The products actually present, prior to carbonation, are 1,3-naphthalenedisodium (83), the result of a meta-orienting influence, and 1,8- and 2,6-naphthalenedisodium, the result of inactivation (which is also the function of a meta-directing influence) of the first ring.

Other examples of inactivation of the ring to which the metal is attached are found in the formation of 4,6-dibenzofurandisodium (48) and 2,2′-triphenylcarbinoltrisodium (29).
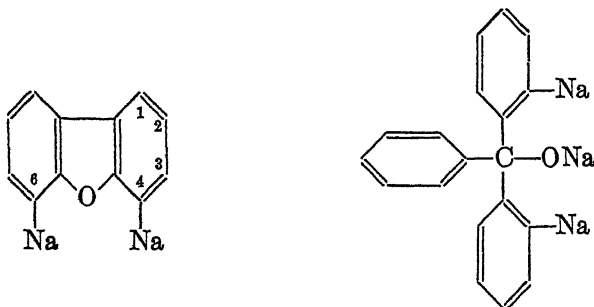
In both instances the second sodium atom enters another rather than the same ring.

Substitution in the m-position implies a meta-directing influence. The principal meta-directing force already known in organic chemistry is a positive pole such as is found in anilinium salts or on the nitrogen atom of a nitro group. Now the only positive pole present in this reaction mixture is the sodium cation. Although bound to the anion by an electrostatic valence only, this ion cannot leave the vicinity of the anion because the operations are carried out either in petroleum ether, which is a non-dissolving solvent for the reagents (amylsodium with phenyl-, benzyl-, or naphthyl-sodium), or in ether, which is virtually a non-dissociating solvent for the metalation of the heterocyclic compound. Hence the cation remains adjacent to the anion and has the same effect as do all positive poles (69) which are attached to the nucleus. The result is a meta-directing influence (88).

A very simple explanation can be given for the fact that the position taken by the metalating group is meta to the directing ion. The positive pole attracts the electrons in the aromatic nucleus and thus reduces the availability in the ring as a whole of the said electrons to other groups or ions needing them in order to become attached to the ring. Now this influence of a positive pole attached to the ring, like the influence of any substituent, whether meta- or ortho-para-directing, will, according to the ordinary principle of conjugation, be greatest in the ortho and para and least in the meta position. Hence the sodium ion in amylsodium, seeking electrons, will have difficulty in acquiring them from phenylsodium but will find less difficulty in the meta position and will, therefore, enter meta to the first metal ion. In short, two strong electron-seeking ions or groups will have little or no tendency to take the conjugated ortho or para positions in an aromatic ring where their like influences would be in maximum com-

petition with each other, but will take the meta position instead. The greater the positive polarity, the greater the percentage of meta substitution.

The only novelty in this meta-directive influence is that the force is attached by coulombic valence rather than by the covalence that exists in the anilinium ion or in nitrobenzene. That an electrostatic bond is no bar to an influence of the cation on the electrons of the anion is shown in inorganic chemistry by the fact that mercuric iodide is colored, although the dissociated iodide ion is colorless; and the color is explained by Fajans (21) as a result of the disturbance caused by the cation on the electrons of the anion. Pauling (100) has illustrated (figure 1) such an effect in a simple case such as that of mercuric iodide. Figure 2

FIG. 1. Normal and deformed ion as pictured by Pauling

FIG. 2. On the left the benzene structure, as given by Pauling, is shown. On the right is a drawing which illustrates the possible changes caused by an adjacent sodium ion. Heavy lines to the ortho and para positions and restricted orbits at these points indicate major pulls on the electrons; lighter lines to the meta positions and moderately restricted orbits are meant to indicate minor attraction. A second sodium ion entering phenylsodium finds electrons more available in the meta than in the ortho or para position.

shows the author's view of the effect of the adjacent sodium ion on the Pauling (100) formula for benzene.

The strength of this meta-directing force of the sodium ion is attested by the fact that it is realized through the methylene group in benzylsodium (88). The product is exclusively meta.

$$C_6H_5CH_2Na + C_5H_{11}Na \rightarrow m\text{-}NaC_6H_4CH_2Na + C_5H_{12}$$
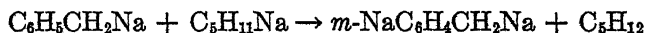
Only the strongest positive charges maintain a high degree of influence across a methylene group. Ingold and coworkers (4, 50, 51, 69) have shown that in nitration a single methylene group invariably reduces the percentage of meta nitration, the amount apparently depending on the strength of the positive pole. The effect of the strong trimethylammonium pole changes from 100 per

cent meta to 88 per cent to 19 per cent as the pole is adjacent, one methylene group, and two methylene groups removed, respectively. The corresponding positions of the weaker nitro group cause 93, 48, and 13 per cent, respectively, of meta nitration.

B. Effect of cation in inhibiting substitution in the anion

In the second class of effects, the ortho–para-directing influence persists but the sodium ion makes metalation more difficult. The phenoxide ion, for example, contains one of the most readily substituted nuclei known, because the inductive (69, 70) and tautomeric (resonance) effects combine to favor substitution. In aqueous solution substitution occurs with extreme rapidity. In a non-aqueous and non-dissociating medium, however, substitution is retarded. The very reactive butylsodium (25), which will metalate benzene very readily, has no action on sodium phenoxide at room temperature even after 3 days' standing. With amylsodium at 55–60°C., substitution will occur in the ortho (87), and to some extent, in the diortho position.[5]

This persistence of the ortho–para-directing force of the oxygen atom, in spite of the positive polarity of the adjacent sodium ion, is not surprising, because the influence of the metal cation on the phenyl nucleus is counteracted by the resonance of the unbound oxygen electrons with those in the ring. The effect is akin to that which occurs in the case of chlorobenzene, where the inductive (70) effect of the halogen atom would normally cause meta substitution, but the tautomeric or resonance effect of the unbound electrons promotes an ortho–para effect. The latter prevails but substitution is more difficult.

If the sodium ion is removed a further distance from the aromatic nucleus, as in sodium benzoxide, $C_6H_5CH_2ONa$, its retardant effect should be even less. This material is, in fact, readily metalated by butyllithium (29) in ether solution, and the position taken by the entering group is ortho.

C. Effect of alkali-metal cation on carboxyl and carbonyl groups

Though not an example of residual polarity, the elimination of the common meta-directing influence of carboxyl and carbonyl groups is, nevertheless, an example of the conversion of such groups into anions by the presence of an alkali metal. Sodium benzoate, for example, is brominated or chlorinated (71) in the ortho position in aqueous solution, and is also metalated by amylsodium (85) in the ortho position in non-aqueous media, though the chief product in this last instance is triphenylcarbinol. In both cases the orienting influence in the anion is ortho. The effect of the sodium ion, adjacent to the anion but relatively far from the phenyl nucleus (and with its electron-attracting influence dampened by the large number of unbound electrons in the oxygen octet), is not sufficient to prevent the orientation which an anion should normally exhibit.

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[5] Recent investigations have disclosed a fair amount of meta substitution also among the disubstituted product (87). The quantity is greater in potassium than in sodium phenoxide. A meta-directing influence is, therefore, not entirely muffled by the screening effect of unbound electrons in the oxygen octet.

Aroylation para to a carbonyl group (see the reaction below) is an example of
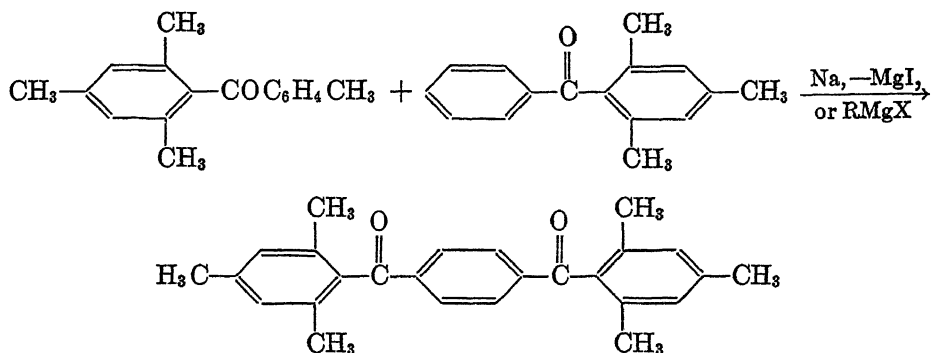
the influence of an alkali metal in transforming the carbonyl group into a point of anionic activity. This reaction, discovered by Fuson (22) and coworkers, takes place under the influence of alkaline catalysts such as the Grignard reagent, sodium, and particularly, magnesious iodide. Addition of the metal to the oxygen end of a sterically hindered carbonyl group is not inhibited (76). Hence a salt is formed, the balance of the polarity in the carbonyl group (caused by comparative electron restraints (69, 70)) is changed, and the entering aroyl group is directed to the para position by an anionic directing influence.

VI. THE ION-PAIR AND DOMINANT CATION IN REACTIONS

Since organometallic salts are so reactive and the metal ion outweighs the anion in activity, the reactions in which the salt participates should be expressed, if possible, so as to show the rôle of the stronger ion. In brief, the reactions should be portrayed as the function of an electrophilic or electron-seeking reagent. Such behavior will be illustrated in the cases of nuclear metalation, side-chain metalation, certain so-called nucleophilic reactions (which, on this basis, are shown to be electrophilic in character), metal–halogen interchange, and disproportionation. The first four reactions concern aromatic systems; the last has to do with an aliphatic one.

A. Nuclear metalation

The action of an organoalkali reagent on an aromatic nucleus is that of a strong electron-attracting cation seeking attachment to the ring. The reaction is aided as much as possible by the anion which receives the displaced proton. This conclusion follows from the fact that the alkali-metal cation attacks the same position as do other electrophilic reagents, such as nitric and sulfuric acids, when it substitutes in a ring which already contains a directing influence, such as a methoxy group.

The number of illustrations where ortho- and para-directing groups cause metalation in the expected position is so large (see table 7) as to constitute conclusive evidence that the ordinary rules of orientation, as applied to the action of electrophilic reagents, hold also with reactive salts, such as the organoalkali reagents

TABLE 7

Substitution in aromatic nuclei containing ortho- and para-directing substituents

1. Directing influence of ethers

COMPOUND	REAGENT	PRODUCT*	REFERENCE
Anisole....	Ethylmagnesium bromide	o-Anisylmagnesium bromide	(13)
Anisole................	Propylmagnesium bromide	o-Anisylmagnesium bromide	(13)
Anisole....	Phenyllithium	o-Lithioanisole	(126)
Anisole...	Butyllithium	o-Methoxybenzoic acid	(25)
Anisole.	Phenylsodium	o-Methoxybenzoic acid	(25)
Anisole.	Amylsodium	o-Methoxybenzoic acid	(86)
Phenetole.......... ...	2-Thienylmagnesium bromide	o-Phenetylmagnesium bromide	(13)
Phenyl ether.	Butyllithium	o-Phenoxybenzoic acid	(25)
Phenyl ether..	Ethylmagnesium bromide	o-Phenoxybenzoic acid	(112)
Phenyl ether.	Phenylsodium	o-Phenylphenyl ether	(80)
Phenyl sulfide..........	Butyllithium	o-Phenylmercaptobenzoic acid	(25)
Phenyl sulfide...... .. .	Phenylsodium	o-Phenylmercaptobenzoic acid	(25)
Benzyl methyl ether ...	Butyllithium	o-Carboxybenzyl methyl ether	(29)
p-Methoxytoluene	Amylsodium	o-Methoxy-m-toluic acid	(97)
p-Bromoanisole	p-Anisyllithium	5-Bromo-2-methoxybenzoic acid	(36)
p-Bromoanisole..... ...	Butyllithium	5-Bromo-2-methoxybenzoic acid	(36)
p-Bromoanisole...... ..	p-Anisyllithium	5-Bromo-2-lithioanisole	(126)
p-Bromoanisole........	Phenyllithium	5-Bromo-2-lithioanisole	(126)
p-Bromodiphenyl ether..	p-Lithiodiphenyl ether	5-Bromo-2-phenoxybenzoic acid	(36)
p-Bromodiphenyl ether..	Butyllithium	5-Bromo-2-phenoxybenzoic acid	(36)

2. Directing influence of amines

COMPOUND	REAGENT	PRODUCT	REFERENCE
Aniline.....	Butyllithium	Anthranilic acid	(29)
Aniline.	Amylsodium	Anthranilic acid	(87)
N-Butylaniline..	Butyllithium	N-Butylanthranilic acid	(29)
Dimethylaniline.... .. .	Amylsodium	N,N-Dimethylanthranilic acid	(25, 86)
Dimethylaniline.........	Methylmagnesium iodide	p-Dimethylaminobenzoic acid	(65)
Dimethylaniline.... ..	Ethylmagnesium bromide	N,N-Dimethylanthranilic acid	(13)
Diphenylamine...	Butylsodium	N-Phenylanthranilic acid	(29)

3. Directing influence of hydrocarbons

COMPOUND	REAGENT	PRODUCT	REFERENCE
Isopropylbenzene.......	Amylsodium	p-Isopropylbenzoic acid	(89)
Biphenyl................	Butyllithium	p-Phenylbenzoic acid	(25)
Biphenyl................	Butylsodium	p-Phenylbenzoic acid	(25)
Biphenyl....	Amylsodium	p-Phenylbenzoic acid	(94)

TABLE 7—*Concluded*

4. Directing influence of alcohols and phenols (as the sodium salt)

COMPOUND	REAGENT	PRODUCT	REFERENCE
Benzyl alcohol.	Butyllithium	o-Carboxybenzyl alcohol	(29)
Benzohydrol	Butyllithium	o-Carboxybenzohydrol	(29)
Triphenylcarbinol	Butyllithium	Triphenylcarbinol-2,2'-carboxylic acid	(29)
Phenol	Amylsodium	Salicylic acid and 2-hydroxy-isophthalic acid	(65)

5. Directing influence when the orienting group is in the ring

COMPOUND	REAGENT	PRODUCT	REFERENCE
Furan.	Phenyllithium	2-Furoic acid	(25, 27)
Furan.	Methyllithium	2-Furoic acid	(25, 27)
Furan.	Amylsodium	2-Furoic acid and 2,5-furandicarboxylic acid	(91)
2-Methylfuran.	Butyllithium	5-Methyl-2-furoic acid	(25)
2-Methylfuran	Phenyllithium	5-Methyl-2-furoic acid	(25)
Thiophene	Ethylsodium	2-Thiophenecarboxylic acid	(107)
Thionaphthene.	Sodium amide	2-Thionaphthenecarboxylic acid	(122)
Thionaphthene.	Ethylmagnesium bromide	2-Thionaphthenecarboxylic acid	(122)
Dibenzofuran	Butylsodium	4,6-Disodiodibenzofuran	(48)
Dibenzothiophene.	Butyllithium	4-Dibenzothiophenecarboxylic acid	(25)
Dibenzothiophene.	Amylsodium	4-Dibenzothiophenecarboxylic acid	(25)
Dibenzothiophene.	Phenylsodium	4-Dibenzothiophenecarboxylic acid	(25)
Carbazole.	Butyllithium	Carbazole-4-carboxylic acid	(34)
N-Ethylcarbazole.	Butyllithium	5-Ethylcarbazole-4-carboxylic acid	(34)
N-Phenylcarbazole . . .	Butyllithium	9-(2',6'-Dicarboxyphenyl)carbazole	(44)

* The product is listed as the acid when the organometallic compound was carbonated, and as the organometallic compound when otherwise treated.

and the Grignard reagent. Methoxy and dimethylamino groups direct the metal exclusively to the ortho position, while alkyl and aryl groups direct largely to the para position.

Only a few exceptions to the influence of ortho- and para-directing groups in metalation are known. Butyllithium, for example, metalates triphenylamine (28) and triphenylarsine (43) in the meta rather than the ortho or para position, in spite of the ortho-directing influence of an amino or arseno group. In view of (1) the much slower rate of, and general resistance to, meta substitution and (2) the fact that when an ortho- and a meta-directing influence are operating

against each other, the ortho outranks the meta, it is logical to suppose that some action has taken place at the nitrogen atom which has extinguished its ortho-directing influence and replaced it by one which permits only the more difficult meta substitution. The only positive pole present in the reaction mixture is the lithium ion in butyllithium. Should it form a complex with triphenylamine—and metal ions in the related Grignard reagent are often regarded as being solvated by the ether and amines used as solvents—a structure like that shown below and resembling somewhat that of triphenylmethylsodium, might be formed. The unbound electrons of the nitrogen atom, which normally would resonate

$$\text{>: N : \overset{+}{Li} \ \overset{-}{Bu}} \qquad \text{<)C:>:} \overset{..}{C}\overset{-}{:} \overset{+}{Na}$$
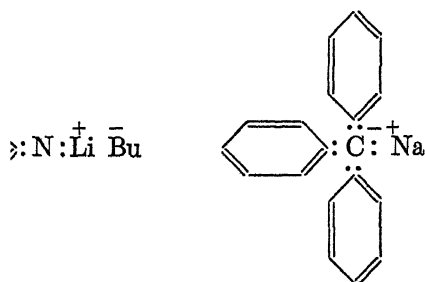
with those in the ring and induce ortho–para substitution, would be restrained by the residual polarity of the lithium ion. The similarity to triphenylmethyl-sodium suggests that the three phenyl groups, which confer such marked acidity upon the hydrogen attached to the central carbon atom, have also conferred on the central nitrogen (or arsenic also) atom an unusual capacity toward forming a comparatively stable salt-like complex with butyllithium, which is sufficiently effective to permit the residual polarity (Section V A) of the lithium ion to act as a meta-directing force.

Phenylcalcium iodide (32) metalates dibenzothiophene in the 3-position, which is meta to the thioether directing group, although phenyllithium (31) and phenylpotassium metalate the same compound in the normal or 4-position. Benzylpotassium (39) fails to metalate dibenzofuran under conditions which are successful for benzylsodium. Both of these results (from phenylcalcium iodide and from benzylpotassium) suggest that a metal ion has become attached in some manner to the compound about to be metalated in such a way as to obliterate the expected ortho substutition and to cause meta substitution, or to inactivate the system so that no metalation occurs. Complex formation is frequently related to the size of the ions involved as well as to their comparative strengths. The particular combinations that would be stable enough to permit such effective control of orientation would not be expected in the usual reactions in which ethers, thioethers, and amines are involved.

Another possible abnormal metalation might be mentioned. When thio-naphthene (122) is dimetalated by sodium amide in hot xylene, some of the product is a 2,3-disodio derivative. Substitution ortho to the sulfur atom would be expected. Entrance of the second metal in the 3-position is unexpected unless one regards that position as activated by an adjacent benz nucleus.

B. Side-chain metalation

Metalation in the side chain can be pictured as an electrophilic (88) process, although in this case there is no orienting influence which makes a comparison with other electrophilic reagents possible. The merit of the electrophilic picture as contrasted with the nucleophilic one can be shown best by stating each in detail.

According to the electrophilic picture, the alkali-metal cation must play the leading rôle, aided as far as possible by the anion, which takes a minor but important part. When, therefore, a toluene molecule collides with the ion pair, the residual polarity in the metal cation attracts the electrons of the carbon-hydrogen covalency in the side chain. The proton is thus loosened by the cation and then taken by the anion. The suggested process is illustrated below with heavy and light arrows indicating major and minor forces:
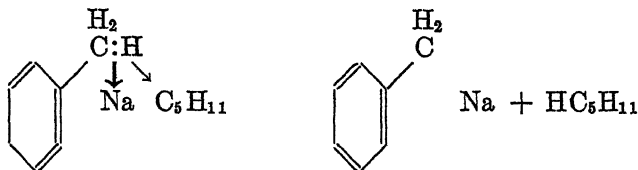
This picture has the advantage of conforming to other evidences of the electrophilic character of organoalkali reagents. It agrees with the evidence for residual polarity in the alkali-metal cation, which in this case should be capable of exerting upon the molecule with which it collides the same type of influence which any positive pole permanently attached to the molecule can effect (compare, e.g., the increased acidity of o- and p-nitrotoluenes) and therefore, at that moment, to labilize the proton by attracting its binding electrons so that formation of a new salt is facilitated. Finally, a joint action of the ion-pair is provided for; and such dual participation, as in the Walden inversion, should proceed with greater ease than would a process which places all of the work on a single ion.

The nucleophilic picture requires that the anion play the leading rôle. The initial and only necessary phase would be:

$$C_6H_5CH_3 + C_5H_{11}^- \rightarrow C_6H_5CH_2^- + C_5H_{12}$$
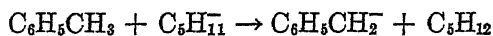
The merit of this view is simplicity; a proton is abstracted, and a new ion is formed. The difficulty is that the picture violates a sense of proportion in that the weaker partner of an ion-pair takes the leading rôle, while the stronger one remains adjacent but idle. In view of the fact that the sodium ion is capable of rendering the electrons in the phenyl and benzyl ions so unavailable that meta substitution results (see Section V A), it would appear unlikely that the sodium ion in amylsodium would release its attraction for the electrons of the amyl ion, and thus permit it to react singly, until a more suitable point for the attractive force of the cation had been found.

Metalation in the side chain rather than the nucleus accords with the expectation that, in general, the product of a substitution will be a salt of the strongest

pseudo acid possible (Section IV A). The margin between nuclear and side-chain metalation may, however, be very slight. Had substitution in the nucleus occurred, the cation would have entered the para position under the directive‧ influence of the alkyl radical (Section VI A). According to the principle that the effect of groups in the acidity of hydrocarbo acids is, in general, in the same direction as that in ammono and carboxylic acids (Section III C), the acidity of $C_6H_5CH_2$—H (K_A for phenylacetic acid is 5.4 × 10⁻⁵) will be higher than that for p-$CH_3C_6H_4$—H (K_A for p-toluic acid is 4.5 × 10⁻⁵). The greater stability of the benzylsodium salt over the isomeric p-tolylsodium is reflected also by the fact that the sodium and potassium salts prepared from p-chlorotoluene rearrange (41) readily, when heated, to the benzylmetal salt. The corresponding lithium salt does not change under the same condition.

The possibility of ortho metalation as well as para has not been considered in this discussion, partly because it occurs either not at all or to a slight extent only (89), and partly because a comparison of the hydrocarbo acid, o-$CH_3C_6H_4$—H, with o-toluic acid (K_A = 1.25 × 10⁻⁴) ·does not provide a fair judgment since, according to Dippy (18), the value for o-toluic acid is abnormally high because of a "limited formation of hydrogen bond."

The chance of side chain $vs.$ nuclear metalation is affected greatly by alkyl groups. The isopropyl (89) group causes the metal to enter the para position and the butyl radical appears also to favor that position, judged by the absence of further side-chain alkylation in the dialkylation of toluene by propyl chloride in the presence of sodium (88, 96).

$$C_6H_5CH_3 + Na + C_3H_7Cl \longrightarrow$$

$$C_6H_5CH_2C_3H_7 \xrightarrow{Na + C_3H_7Cl} p\text{-}C_3H_7C_6H_4CH_2C_3H_7$$
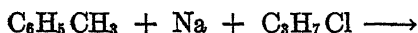
C. The so-called nucleophilic reactions

A nucleophilic reagent (70, 121) is ordinarily understood to be one which reacts in a manner opposite to that of an electrophilic one, i.e., by introducing an electron-donating rather than an electron-attracting group. Hence meta-directing groups—for example, nitro—will cause such reagents to substitute in the ortho or para position, as indicated below:

$$C_6H_5NO_2 + KOH \xrightarrow{\text{O}} o\text{-}HOC_6H_4NO_2$$

That nucleophilic reagents, the opposite of electrophilic reagents, should exist, is eminently reasonable. That the above and similar reactions are good examples of the action of nucleophilic reagents is questioned. Potassium hydroxide or methoxide is the salt of a very weak acid and an active alkali metal. According to the arguments presented in this paper, such reagents are by nature electrophilic. Unless the environment favors dissociation—and many of these reactions are carried out in non-aqueous solvents or at high concentration—or other factors intervene to insure the reaction of the hydroxide or alkoxide ion only, the cation should play the leading role.

The electrophilic character of this reaction does, indeed, appear most reasonable. The first step consists of a 1,4-addition—a process which is merely one of the common reactions of salts (see Section IV B)—in which the cation seeks the position of maximum electron density, and does so the more readily as the cation becomes stronger (KOH > NaOH). The second phase is restoration of the conjugated ring system by an elimination (loss of alkali hydride) or oxidation process.

The additive character of the reaction has long been recognized. In 1902, Meisenheimer (82) observed that potassium methoxide in 5 per cent methanol (approximately 0.7 normal) added to 9-nitroanthracene. The addition product, when boiled with ethyl alcoholic potassium hydroxide, was converted to the oxime of an acetal, by steps which are pictured below.
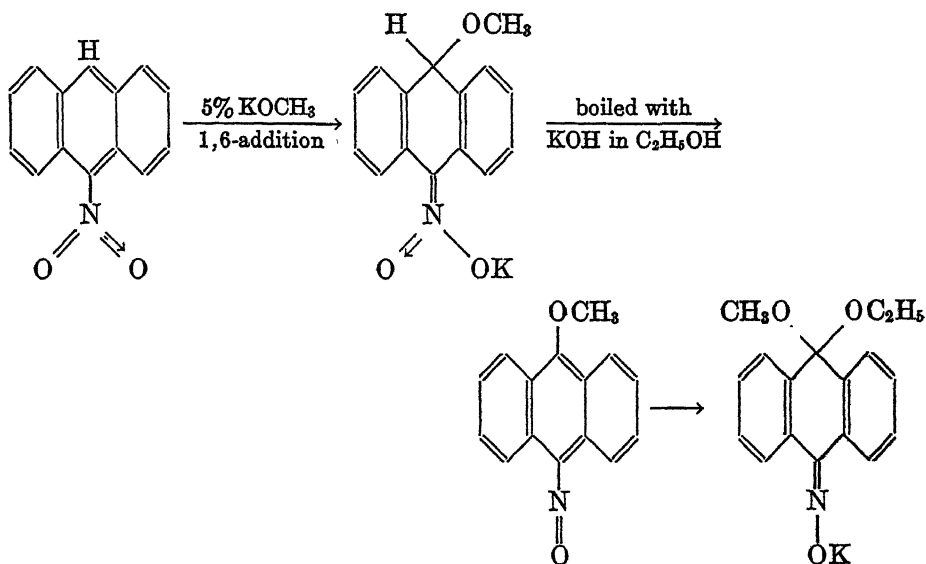
The addition of sodium methoxide to trinitrophenetole has also been regarded (82) as an addition process.
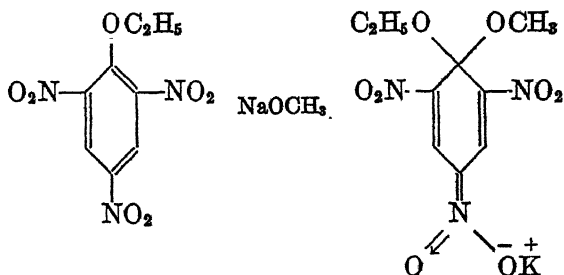
The relation which these additive processes have to other similar additive processes (6, 75) is clearly shown in table 8. The first two examples show the addition of alkyllithiums (138) and sodium amide (118) to the C=N bond in

LiR in toluene

heat −LiR

$NaNH_2$ in toluene or dimethyl-aniline

heat −NaH

$NaN(C_6H_5)_2$ in liquid ammonia

(1) O
(2) −NaOH

5 per cent $KOCH_3$ in CH_3OH

−KOH (without oxidation)

solid KOH warmed

(1) O
(2) −KOH

KOH (150 g.) water (37 g.) $KClO_3$ at 210–300°C.

(1) $KClO_3$
(2) −KOH

C_6H_5MgX

(1) O
(2) −HOMgX
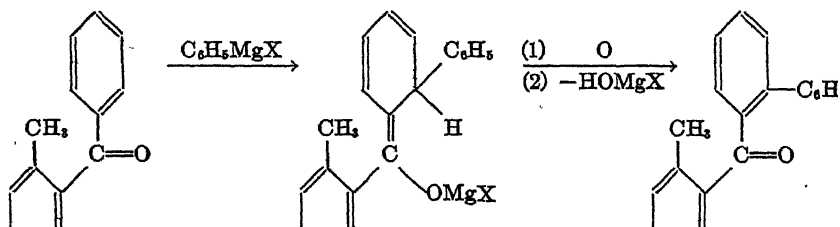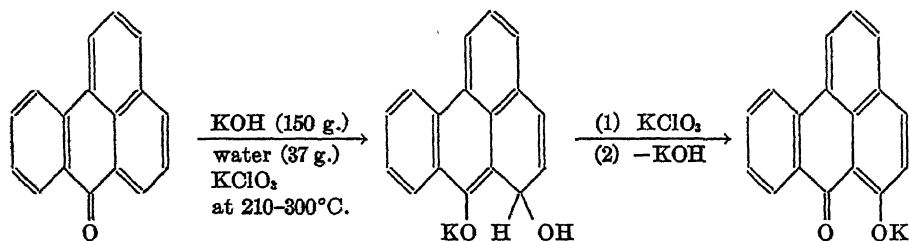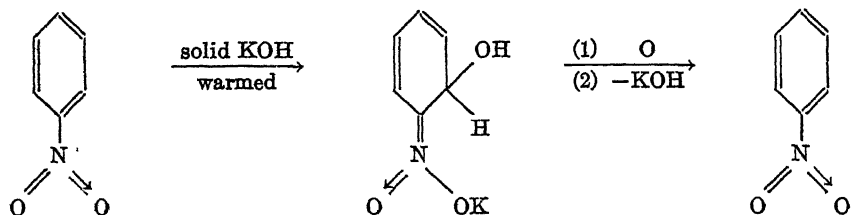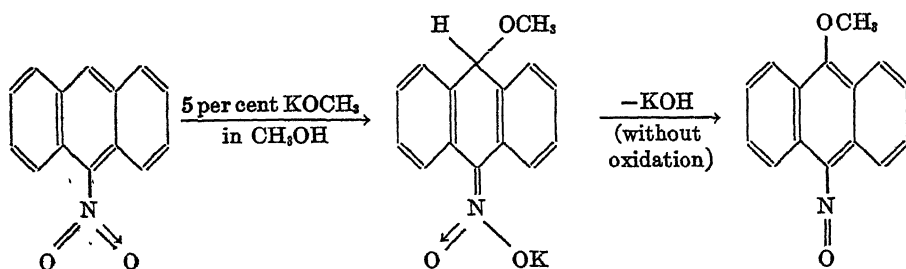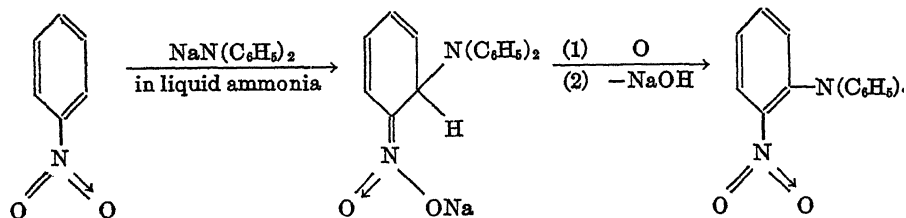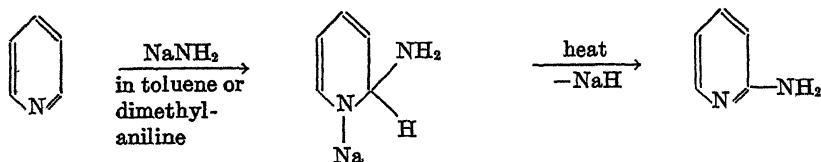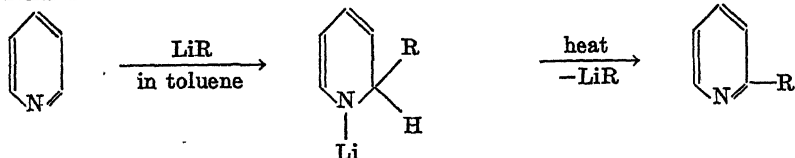
pyridine. At higher temperatures lithium hydride and sodium hydride are split off, so that the net result is the alkylation and amination of pyridine. In the third example, sodium diphenylamide (7) undergoes 1,4-addition with nitrobenzene in liquid ammonia. The dihydro product then either eliminates sodium hydride or loses hydrogen by oxidation with excess nitrobenzene. The net result of the process is an amination—substitution of diphenylamine in this instance—of nitrobenzene. In the fourth example, a step in the reactions observed by Meisenheimer (82) is shown, the addition being across the 1,6-positions, and the process being completed by thermal elimination of potassium hydroxide. The fifth example is the reaction of powdered potassium hydroxide with nitrobenzene (127). The conjugated ring system is restored by oxidation by air or nitrobenzene. The net result is hydroxylation. Similarly, mesobenzanthrone reacts with potassium hydroxide and aqueous potassium chlorate at 210–310°C. to give 4- and 2-hydroxymesobenzanthrones (9) by steps similar to those of the other reactions. Finally, phenylmagnesium bromide adds in the 1,4-positions to benzoylmesitylene (23), because the normal addition across the carbonyl group is impeded by steric hindrance. Oxidation of the enol addition product by air restores the aromatic system.

These reactions are essentially the same with respect to the first step. The reactive salts show an electrophilic character. The dominant and electron-seeking cations attach themselves at the position of greatest electron density in the molecule; the alkyl, amino, alkoxy, and hydroxy groups take the 2-, 4-, or 6-position remote from the position of the metal ion; and the net result—after thermal decomposition, or oxidation by air, nitrobenene, or perchlorate—is alkylation, amination, alkoxylation, or hydroxylation of the nucleus. Representation of such processes as nucleophilic gives a wrong impression, for the term "nucleophilic reagent" implies the opposite of an electrophilic reagent. In reality, the nature of the reagent has not changed; only the manner in which the reagent reacts is different. The dominance of the cation, so clearly evident in other reactions, is not extinguished merely because the reaction is an addition, rather than a substitution, process.

D. Metal–halogen interchange and related effects

The interchange of metal and halogen arouses more than ordinary interest

$$\text{(ring)}\underset{\text{OCH}_3}{\overset{\text{I}}{}} + \text{C}_4\text{H}_9\text{Li} \longrightarrow \text{(ring)}\underset{\text{OCH}_3}{} + \text{C}_4\text{H}_9\text{Br}$$
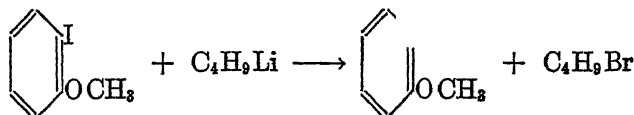
because the reaction normally expected would lead to a Wurtz product and sodium halide. The interchange has been observed a few times (33, 101, 104, 131) with aliphatic compounds and has been found to be reversible (33) in some cases. The chief interest, however, has been in the aromatic series (37, 126). In general, an interchange occurs readily with iodides, to some extent with bromides, and little, if any, with chlorides (79, 84).

Although the reason for an interchange rather than a Wurtz reaction cannot be specified, the effect in the aromatic series can be related to the activating influence of the groups involved. According to such a plan, the alkali-metal cation will play the same rôle as does any strong electron-attracting group. In order to appreciate this rôle, it is necessary to present a brief discussion of the general phenomena involved and then to show the way in which the metal cation fulfills expectations.

Strong electron-attracting groups, such as nitro, diazonium, and alkyl-substituted ammonium, have long been recognized as promoting the replacement of an ortho or para halogen atom by a strong electron-donating group such as methoxy, phenoxy, hydroxy, amino, and the like. This type of activity will be designated as type I. The converse of this rule (type II activity) is that strong electron-donating groups, such as methoxy or dimethylamino, will promote the replacement of an ortho or para halogen atom by a strong electron-attracting group, such as nitro or an alkali-metal ion. These rules are represented graphically below:

Type I active state

Strong electron-attracting groups: NO_2, $\overset{+}{N_2}X$

Labile groups: Cl, Br, I, NO_2

NaOCH₃ or HNC₅H₁₁

Type II active state

Labile groups: Br, I

Strong electron-donating groups: OCH_3, $N(CH_3)_2$

RLi
HNO₃

Strong electron-attracting groups

Strong electron-donating groups

Stable state
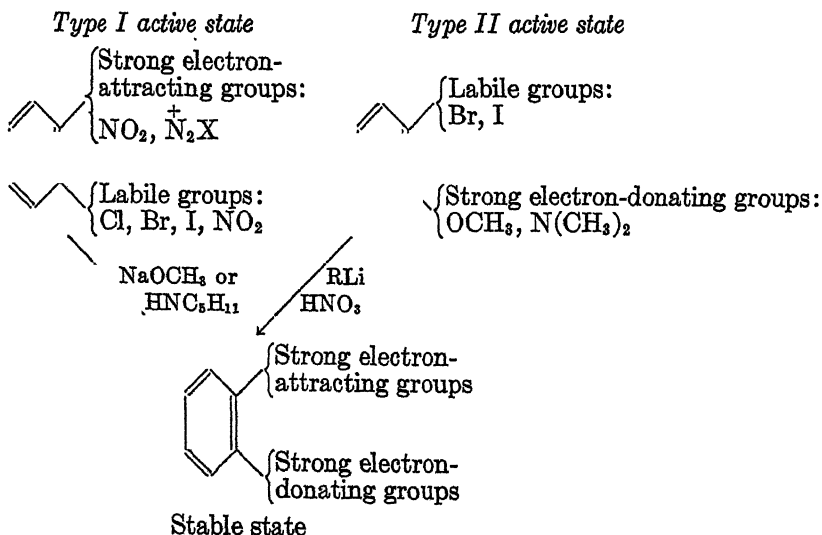
These statements accord with the general view (10) that nitro and methoxy groups have opposite activating effects when substituted in the aromatic nucleus. The halogen atoms are between the two extremes. With appropriate reagents the halogen atom can sometimes be removed and replaced by a group which will neutralize the effect of the one already in the nucleus. Other active groups besides the halogen, such as a nitro group adjacent to a nitro group, are replaced by a methoxy or an electron-donating group. In any event, the system progresses toward the stable state of two highly activating groups of opposite kind, neutralizing the effect of each other. The reaction is obviously best realized in the ortho and para positions where the groups are in a vinylogous relation, and of these two positions the ortho is frequently the most reactive, possibly because the distance between activator and activated is less than in the para position.

Examples in the type I class are very numerous. The activation of a halogen atom ortho to a nitro group has long been known and has been studied (16) extensively. Sodium hydroxide, sodium alkoxides, sodium phenoxides, piperidine, and the like can be used for the reaction. The lability of a halogen atom ortho to a diazonium group (98, 108) is also common. The number of examples of these types of activation which could be listed are too numerous to tabulate in this paper. It is sufficient to state that the reactions are well known and to give an example in table 9 for the sake of comparison. Similar statements can be made with respect to the activation of a nitro group ortho or para to another nitro group (16) or a diazonium (5) ion. The nitrile (63) group also causes an ortho, nitro, or halogen atom to be replaceable.

The comparable case with the organoalkali compounds would be that of a halogen activated by a metal cation in the ortho position, for if such a juxtaposi-

TABLE 9

Examples of activation of a halogen atom ortho to a positive pole
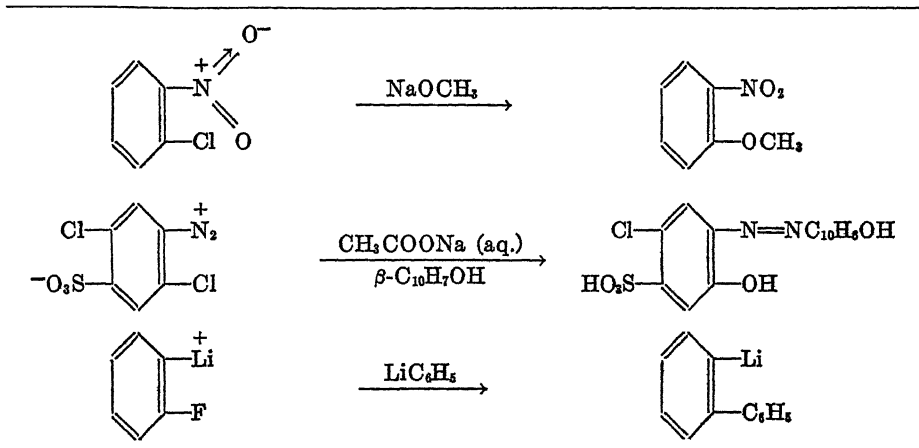
tion of halogen and cation could be realized, the strong electron attraction of the latter should permit easy replacement of the halogen by a group which would be more suitable than the halogen. The situation is, of course, rare, because of the difficulty of introducing a metal ortho to a halogen without metathesis. Yet one well-defined case is known.

Wittig (125) and coworkers have found that the reaction of phenyllithium with the four monohalobenzenes gives 8, 10, 8, and 70 per cent yields of biphenyl from the iodo, bromo, chloro, and fluoro compounds, respectively. The high yield with the fluoro compound is interpreted as meaning that metalation of fluorobenzene first occurs. The fluorine atom is made active by the adjacent

$$FC_6H_5 + LiC_6H_5 \rightarrow o\text{-}FC_6H_4Li + C_6H_6$$
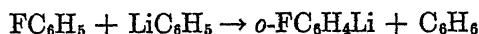
lithium ion so that it reacts readily with more phenyllithium. Proof of

$$o\text{-}FC_6H_4Li + C_6H_5Li \rightarrow o\text{-}LiC_6H_4C_6H_5 + LiF$$
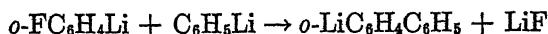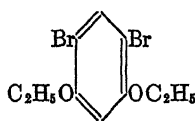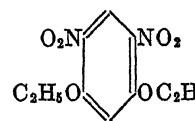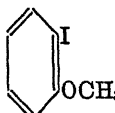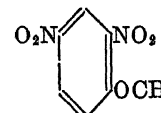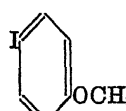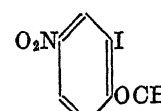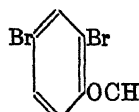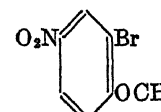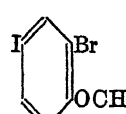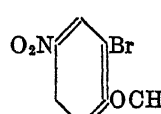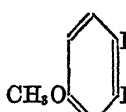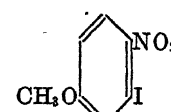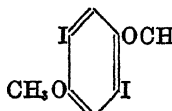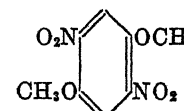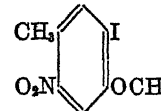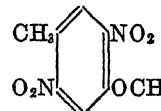
TABLE 10

Examples of nitro–halogen interchange

NITRO-HALOGEN INTERCHANGE		REFERENCE
Br–[ring]–Br, C_2H_5O–[ring]–OC_2H_5 $\xrightarrow[\text{fuming}]{HNO_3}$ O_2N–[ring]–NO_2, C_2H_5O–[ring]–OC_2H_5		(73)
I–[ring]–OCH_3 $\xrightarrow[HNO_3]{\text{fuming}}$ O_2N–[ring]–NO_2, –[ring]–OCH_3		(74)
I–[ring]–OCH_3 $\xrightarrow{HNO_3}$ O_2N–[ring]–I, –[ring]–OCH_3		(102)
Br–[ring]–Br, –[ring]–OCH_3 $\xrightarrow{HNO_3}$ O_2N–[ring]–Br, –[ring]–OCH_3, Br		(8)
I–[ring]–Br, –[ring]–OCH_3, Br $\xrightarrow[HNO_3]{\text{fuming}}$ O_2N–[ring]–Br, –[ring]–OCH_3, Br		(62)
–[ring]–I, CH_3O–[ring]–I $\xrightarrow{HNO_3}$ –[ring]–NO_2, CH_3O–[ring]–I		(103)
I–[ring]–OCH_3, CH_3O–[ring]–I $\xrightarrow{HNO_3}$ O_2N–[ring]–OCH_3, CH_3O–[ring]–NO_2		(103)
CH_3–[ring]–I, O_2N–[ring]–OCH_3 $\xrightarrow{HNO_3}$ CH_3–[ring]–NO_2, O_2N–[ring]–OCH_3		(103)

the formation of a lithiofluorobenzene is furnished by decomposing the reaction product (fluorobiphenyl) with benzophenone instead of with water. *o*-Phenyltriphenylcarbinol is formed.

$$o\text{-LiC}_6H_4C_6H_5 + (C_6H_5)_2CO \rightarrow o\text{-}C_6H_5C_6H_4C(OH)(C_6H_5)_2$$
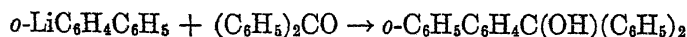
No evidence could be found that amylsodium causes a similar metalation of chlorobenzene, for the products of carbonation contained no trace of *o*-chloro-

benzoic acid (90). It is clear, however, from Wittig's work that a metalation is possible in reactions of organoalkali compounds with aromatic halogen compounds, and that the halogen atom in the ring is activated by an adjacent cation.

Activity in the type II class will be illustrated by reactions which are the exact opposite of two of the three typical examples shown in table 9 for type I activity. These examples will show nitro–halogen and metal–halogen interchange. An exact opposite of the diazonium-activating influence cannot be given, for the obvious reason that there is no reagent for introducing the diazonium ion directly into the nucleus.

Nitro–halogen interchange, that is, replacement of a halogen atom ortho or para to a methoxy group by a nitro group, occurs frequently enough to warrant the conclusion that the reaction is a characteristic phenomenon. The process is all the more remarkable because it often occurs in spite of the tendency for nitration in some other position. Some examples of nitro–halogen interchange are shown in table 10.

The ease of the reaction of the diethyl ether of dibromoresorcinol with fuming nitric acid is in contrast to the lack of reactivity with a reagent which would introduce another ethoxy group. Heating in a sealed tube to 100°C. with sodium methoxide and to 230°C. with sodium phenoxide effects no replacement of halogen. In some of the other illustrations the halogen halide eliminated caused substitution in another position in the ring under the oxidizing influence of nitric acid. Nitro–halogen interchange is seen to be comparatively common and the iodine atoms appears to be more reactive than the bromine.

In a similar way, metal–halogen interchange neutralizes the effect of an electron-donating group by an electron-attracting group, usually in the ortho and para positions. Some compounds which undergo this interchange of lithium for a halogen when allowed to react with butyllithium are shown below. The halogen atom replaced by metal is shown in heavy type.
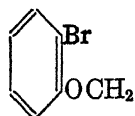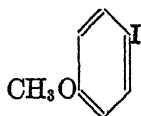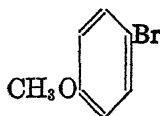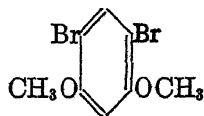
Reference.........(36)   (37)   (37)   (126)
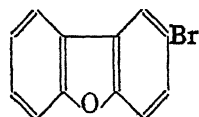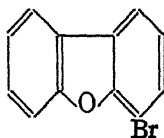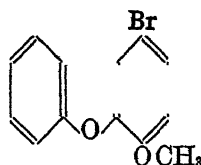
Reference..........(47)   (47)   (45)

3-Bromobenzofuran also undergoes the metal–halogen interchange with butyllithium. This reaction is unusual because the halogen is meta to the activating linkage. The tendency for the electron-attracting group to occupy a position where it will be better able to neutralize the electron-donating group is shown,

however, by the fact that, after carbonation, the products are found to be 3-
and 4-carboxydibenzofurans (47).

As might be expected, interchange takes place also when the dimethylamino
group is present. Either a metal ion (24) or a nitro group (130) will replace
bromine.

$$(CH_3)_2N\text{-}C_6H_4\text{-}Br \xrightarrow{LiBu} (CH_3)_2N\text{-}C_6H_4\text{-}Li + C_4H_9Br$$

$$(CH_3)_2N\text{-}C_6H_4\text{-}Br \xrightarrow{NaNO_2} (CH_3)_2N\text{-}C_6H_4\text{-}NO_2 + NaBr$$
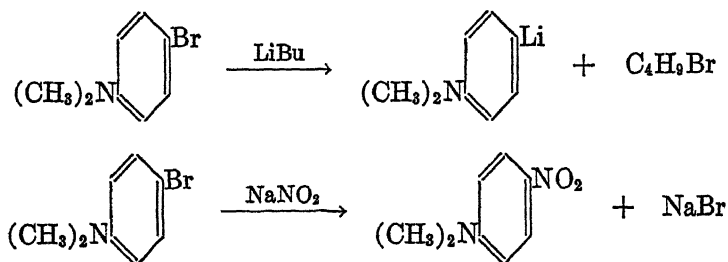
Replacement of a halogen atom by a metal cation has been observed also in
the reaction of p-iodotoluene (33) with phenyllithium and of α-bromonaphthalene
with a number of alkyllithium compounds. m-Bromodimethylaniline (38) also
undergoes some replacement. The most characteristic cases, however, are those
in which a methoxy or ether linkage activates the halogen in the ortho or para
position.

The activation by a methoxy or dimethylamino group must not be confused
with those reactions in which a hydroxy, amino, or other group with a replace-
able hydrogen causes a replacement. The process with these latter groups ap-
pears to operate by an initial substitution of the hydrogen of the hydroxy or
amino group and then by a rearrangement (17) to force a replacement of the
nuclear atom. A large number of such indirect substitution reactions are known.

E. Disproportionation

When an organoalkali compound reacts with an organic halide, cleavage takes
place and coupling and disproportionation occur. In disproportionation the
saturated product comes from the organometallic compound; the unsaturated
one or its equivalent from the halide. Representative equations are:

$$C_5H_{11}Na + C_4H_2Cl \qquad C_5H_{12} + C_4H_6 + NaCl$$

$$C_3H_7Na + (CH_3)_3CCH_2Cl \qquad C_3H_2 + (CH_3)_2C\overline{\text{—}CH_2\text{—}CH_2}$$
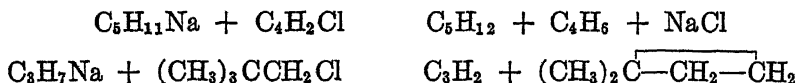
Proof of this statement rests on two independent studies: one an analysis (84)
of the products from the reaction of amylsodium and octylsodium with ethyl,
propyl, butyl, and hexyl chlorides, bromides, and iodides and the other a study
(124) of the reaction of ethylsodium with hexyl chloride and of propylsodium
with neopentyl chloride. Except for some metal–halogen interchange (84) that
occurs, the products are in accordance with the above rule.

The explanation of disproportionation from the viewpoint that the organo-
sodium compound is an electrophilic reagent is that the metal cation seeks the

point of highest electron density in the alkyl halide—namely, the halide atom. In the ensuing system of sextets and open octets, the space relationships are such that the hydrogen on the β-carbon atom of the alkyl halide (or the hydrogen atom of the γ-carbon atom if none is available in the β-position) shifts to the ion originally attached to the metal cation. This sequence of changes may well be so near to each other as to be practically simultaneous. Possible steps are shown below:

$$\overset{+}{Na} \quad Cl \qquad \qquad \overset{+}{Na} \quad Cl$$

$$H_2C \quad \quad CH_2 \qquad H_2C \qquad \qquad +CH_2 \qquad H_2CH + CH_2$$

$$HCH \qquad R \qquad H \qquad \qquad R \qquad CH$$

$$R' \qquad \qquad CH \qquad \qquad R'$$

$$R'$$
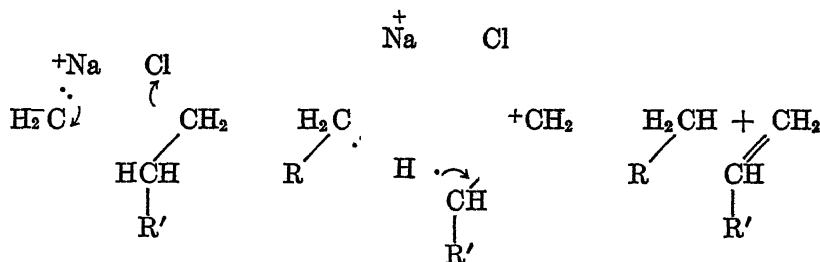
The process is an interesting one because free-energy data (99), given below,

	FREE ENERGY
Ethylene..	+12,300
Ethane..	−10,700
Butane..	−6,200
Trimethylethylene.................................	+13,700
Pentane...	−8,600
Decane..	−2,900

suggest the unlikelihood (93) of a disproportioning as compared with a coupling reaction. Experimental facts show that disproportionation is usually the common reaction. The discrepancy is reconciled by the mechanism pictured. In the formula below, the distance, a, required to be bridged for the coupling

$$\overset{+}{Na} \qquad Cl$$

$$H_2C \qquad \qquad b \qquad \qquad CH_2$$

$$R \qquad H$$

$$CH$$

$$R'$$
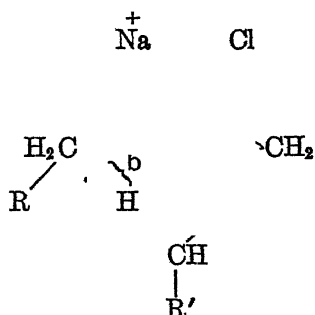
process, is greater than the distance, b, over which the hydrogen atom must travel to effect disproportionation. The force tending toward coupling is therefore disadvantageously disposed, as compared with that for disproportionation.

When disproportionation (84) occurs between an arylsodium and an alkyl chloride, the aromatic hydrocarbon and an olefin are formed. The rapidity with

which the olefin is formed reduces the chances of higher degrees of polymerization. When disproportionation occurs between an alkylsodium and an aryl

$$C_6H_5Na + C_5H_{11}Cl \rightarrow C_6H_6 + C_5H_{10} + NaCl$$
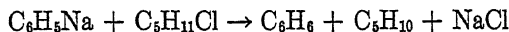
chloride, the unsaturated product is o-phenylene, which cannot undergo intramolecular stabilization and therefore adds alkylsodium or undergoes polymerization with another molecule of o-phenylene. Polymers and all higher molecular weight compounds will be exclusively aromatic or composed of more aromatic

$$\xrightarrow{RNa^*} RC_6H_4Na \xrightarrow{C_6H_5Cl} \text{Metathesis or disproportionation}$$

$$\xrightarrow{+C_6H_4} {}^-C_6H_4C_6H_4^+ \xrightarrow{RNa} \text{Addition followed by reaction with more chlorobenzene, etc.}$$

$$\xrightarrow{2C_6H_4+} C_{18}H_{12}\dagger$$
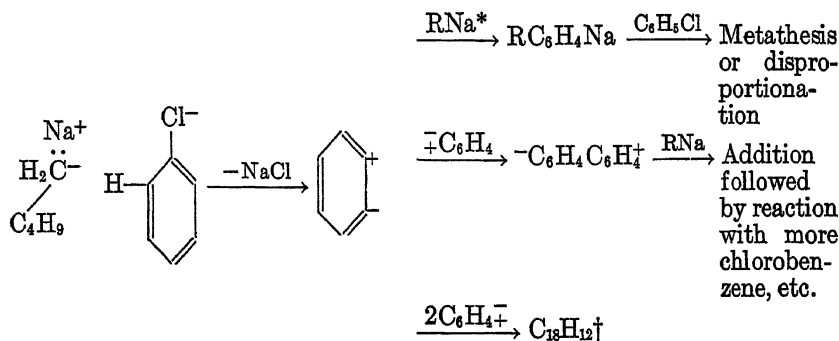
* R = C_5H_{11} † Triphenylene

than aliphatic radicals. Ortho products predominate in the numerous combinations possible.

The process of disproportionation bears some similarity (123, 124) to the elimination reaction in that an alkyl halide is converted to an olefin. The common interpretation (68) of the latter process is that proton elimination is the first step in the reaction, and chloride-ion elimination is the second. The explanation of the process which the organoalkali (88) reagent induces is that the steps may well be simultaneous but if there is any order, chlorine elimination precedes rather than follows proton transfer. The contrasting features in the interpretations are illustrated below (equations 1 and 2) in the formation of pentene from amyl chloride:

(1) $C_3H_5CH_2-CH_2Cl \quad \underset{\text{proton abstraction}}{\xrightarrow{C_2H_5O^-}}$

$$C_3H_5CH-CH_2Cl \xrightarrow[\text{chlorine elimination}]{-Cl^-} C_3H_5CH=CH_2$$

(2) $C_3H_5CH_2-CH_2Cl \xrightarrow[\text{chlorine elimination}]{NaR}$

$$C_3H_5CH_2-CH_2^- \xrightarrow[\text{proton removal}]{-H} C_3H_5CH=CH_2$$
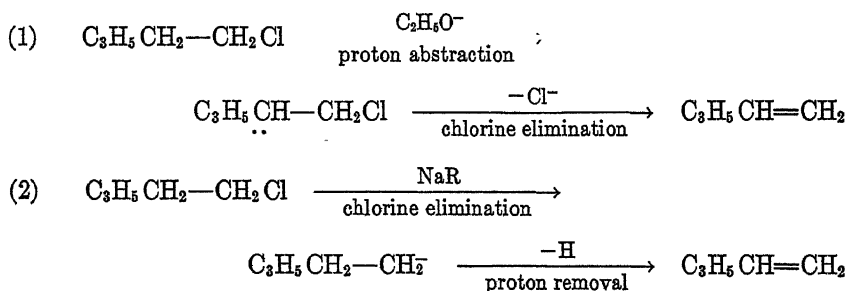
The condition of the reagent that causes elimination can be markedly different in the two processes. In the former, the ions are dissociated in alcohol or aqueous alcohol so that the reaction can be that of the individual ions. The anion, as a base, takes a proton. Chlorine is eliminated as an ion. In the latter, the solvent

is non-dissociating and in some cases non-dissolving. The ions of the organo-metallic reagent are therefore adjacent. In such a condition, the sodium ion exerts a powerful attraction for the electrons of the anion. In the absence of a solvating agent, which would offer a multitude of electrons for the cation, it is unreasonable to suppose that this ion will release its attraction and permit the alkyl anion to acquire a proton, before it has found other electrons which satisfy better its attractive force.

VII. ELIMINATION OF THE METAL-ION INFLUENCE

Dissociation of the ions is, obviously, one of the principal factors which can have a bearing on whether the alkaline salt acts as an ion-pair or as individual ions. In the former state the reagent should, by the interpretation used in this paper, serve as an electrophilic reagent. In the latter state, it could function as a nucleophilic one.

TABLE 11

Comparison of conductivities of salts in ether, pyridine, and water

SALT	SOLVENT	DIELECTRIC CONSTANT	DILUTION VOLUME L	EQUIVALENT CONDUCTANCE
Triphenylmethylsodium..............	Ether	4.7	13.9	0.073
			381.	0.0053
Triphenylmethylsodium.............	Pyridine	12.5	3900.	19.2
Triphenylmethylpotassium...........	Pyridine		2400.	19.2
			6020.	19.4
Lithium iodide.....................	Ether	4.7	437.	0.042
Lithium iodide...	Water	81.1	1024.	110.3

When the salt is insoluble, as in the case of amylsodium in petroleum ether, the ions must be adjacent to each other and not dissociated. The reactions would preferably be those of an ion-pair. Neither is there much likelihood that soluble compounds, such as butyllithium, will dissociate in petroleum solvents, because of the extremely low dielectric constant of this medium.

When the reagent is dissolved in ethyl ether the possibility of the dissociated ions, instead of the ion-pair, effecting the reaction must be considered, because solutions in this solvent often conduct the electric current. Nevertheless good reasons can be advanced for favoring the ion-pair behavior: (1) the dissociation must be very slight because the conductance is so low, and (2) the potassium salt of triphenylmethyl reacts many times faster than the sodium salt.

The degree of dissociation of salts in ether as compared with other solvents can be judged from the data in table 11, recorded by Ziegler and Wollschitt (137).

The data in table 11 show that the difference between the conductance of lithium iodide in ether, where the ions are partially dissociated, and that in

water, where they are completely dissociated, is approximately 2500 fold.   The conductance of triphenylmethylsodium is of the same general order of magnitude as is that of lithium iodide, but shows the abnormal behavior of having a maximum conductance before infinite dilution is reached.   If these values are regarded as furnishing a fair basis for a rough approximation of the proportions of ion-pairs and dissociated ions, the conclusion would be drawn that the latter may be present to the extent of a little less than 0.05 per cent of the total amount of organoalkali compound present.   If the adjacent cation causes the ion-pair to have a reactivity different from that of the dissociated ion, the latter would have to be approximately 2600 times as reactive in order to have an equal share in the reaction and even more reactive if largely responsible.   If the behavior of the anion is unaffected by the adjacent cation, these differences would, of course, have no significance for the problem at hand, except in so far as the probability of contact is affected.

That the rôle of cation in ether solution need not be that of an inert partner, even in salt–acid interchange, is indicated by the fact that Conant and Wheland (15) found that α-naphthyldiphenylmethylsodium required about a month in order to reach equilibrium with diphenylbiphenylmethane in ether, whereas the potassium salt needed but a few hours.   They noticed that an abnormal decoloration, which took place instantaneously when α-naphthyldiphenylmethylpotassium reacted with triphenylmethane, required a few minutes to several months when the corresponding sodium salt was used.   These results, together with the evidences of residual polarity and the satisfactory explanation offered for reactions of organoalkali compounds, are consistent with the view that a strong cation can create a disturbance in the electrons of the anion so that, in effect, it plays a definite part in the reactions which involve anions.   Certainly, no serious error in proper representation of the processes in ether would appear to be made if the reactions were always expressed as the work of an ion-pair rather than that of the anion only.

Attention has been called (table 11) to the fact that the conductivity in ether solution is higher in concentrated than in dilute solution.   This result might be interpreted as indicating complex ions.   The equation below represents the complex ion in its simplest form and the solvated cation.

$$(C_6H_5)_3CNa + (C_6H_5)_3CNa + (C_2H_5)_2O \rightarrow [(C_6H_5)_3CNa(C_6H_5)_3C]^- + [Na:O(C_2H_5)_2]^+$$
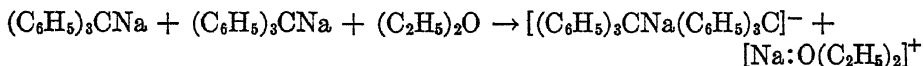
If such a condition exists there might be some question as to whether the complex anion so formed would be appreciably more reactive than the ion-pair from which it is produced; but should it be more reactive there would appear to be good reason for doubting that it is over 2000 times more reactive.

It is true that there are some instances where reactions (40) have been shown to be somewhat faster in the slightly dissociating solvent, ether, than in the non-dissociating one, petroleum ether.   Isobutyllithium and butyllithium (39) are relatively weak metalating agents in petroleum ether but are effective in diethyl ether.   Diphenyl ether with butyllithium (25) gave only a 7 per cent yield of the

2-lithio product in petroleum ether but a 54–60 per cent yield in ethyl ether. These differences cannot at present be credited with certainty to the slight amount of ionization that is present in ether as compared with none in petroleum ether. Variations in boiling points of the reaction mixtures, in concentrations of reagents, or degrees of association may equally be responsible for all such effects. Two different ethers may, in fact, show an equally large variation. Butyllithium (39), for example, metalates dibenzofuran better in dibutyl ether than in ethyl ether.

In alcohol and acetone solutions the salts are dissociated, more so than in pyridine, in which, according to table 11, triphenylmethylsodium is somewhat dissociated, i.e., about one-fifth the maximum possible. Reactions in such solvents may, therefore, be the work of individual ions rather than ion-pairs.

In such media, the reagent may be regarded either as nucleophilic or electrophilic, according to the character of the other reactant, the comparative activity of the undissociated salt and the dissociated ion, or probably the concentration of the reagents.

VIII. CONCLUSION

At the beginning of this paper the current opinion, that organoalkali compounds are salts, was made the basis for a series of premises for connecting (1) the chemical behavior of these compounds with that of the chemistry of salts in general and (2) the activity of the cation with that of strong electron-attracting groups. Enough illustrations have been given to show that the behavior of these and related compounds can be interpreted from these viewpoints. The field is very broad. Space does not permit inclusion of many other examples that are compatible with these ideas.

An alternative view that the strong cation confers high reactivity upon the anion, which in turn acts as the principal reagent in the reaction, could have been developed. This paper must not be construed as denying such a possibility. Something might, in fact, be said in favor of the view that a hydrocarbo ion, which could attain a stable state by acquiring a proton and thus changing to a hydrocarbon, would act as a strong driving force in any reaction. Yet such a view involves an indirect rather than a direct approach to the problem. The cation activates the anion; the anion then effects the reaction. No account is taken of the fact that in metalations, for example, the strong tendency of the anion to acquire a proton can be realized only by severance of a proton from another hydrocarbon; and consideration of the net energy change in such a process might go far toward dispelling the illusion created by viewing only the affinity of a hydrocarbo base for a proton. Nor is any explanation readily apparent as to how a cation can be active enough to create or maintain an unusually reactive anion, and at the same time be so inactive as to fail to have an effect upon the compound with which the anion or salt is reacting. The capacity of a cation of such activity to pick out or create positions of maximum electron density in any system with which the ion-pair is in contact, and thus to stimulate formation of a new salt, is overlooked.

This review has not considered also the possibility that the organoalkali compounds are partly covalent in character. This supposition has much to recommend it. The lithium compounds have many properties that indicate that the bond between the metal and the organic radical is covalent. But presentation of the subject under the supposition that covalency plays a fractional part in the reactions of all organoalkali compounds involves more difficulties than the view that electrovalency and covalency are merely two extremes of binding (21), differing in degree, not in kind. On the other hand, correlation of the chemistry of the distinctly polar organosodium compounds with that of the chemistry of such organic compounds as nitrobenzene and anilinium salts (cf. orienting influence) covers all intermediate cases such as may exist with the lithium compound.

In any event, there are well-defined cases such as the orienting influence of the sodium ion, the directive influence of ortho-para-directing groups on metalation, and the interchange reactions, where the behavior is explicable on the same grounds which have long been conventional in organic chemistry. In order to make this correlation, the simple concept of an ion-pair and of a dominant cation, which serves as does an active substituent, fits admirably. As long as the physical conditions under which the reagents operate keep the members of the ion-pair together, the distinction between electrovalence and covalence has no great significance in a large number of cases. Only when solvation, dilution, or some other factor permits the ions to fall apart does the difference between the two types of valence become meaningful. Interpretations on the basis of the simple premises set up at the beginning of this paper—namely, that the organoalkali compounds are salts, whose activities are proportioned to the differences in strengths of the acid components and metal from which the salt is theoretically derived, and whose reactions are characterized by the degree of dominance of the cation—are, therefore, adequate for all known facts related to the organoalkali compounds.

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NETWORK STRUCTURE AND THE ELASTIC PROPERTIES OF VULCANIZED RUBBER[1]

PAUL J. FLORY

The Goodyear Tire and Rubber Company, Akron, Ohio

CONTENTS

I. INTRODUCTION

As early as 1859 Joule recognized on the basis of his experiments that the retractive force in stretched rubber originates from thermal motions as apart from intermolecular attractive forces. In the language of thermodynamics, the Gough–Joule effect (increase of tension in stretched rubber with temperature, or the thermodynamically related temperature rise during adiabatic stretching) demonstrates that the extension of rubber is accompanied by a decrease in entropy. More recent experimental measurements on the thermoelastic properties of rubber (1, 15, 28, 31) have shown explicitly that this increase in entropy is largely responsible for the retractive force, the change in internal energy with elongation being of minor importance. The problem of rubber elasticity is chiefly concerned, therefore, with an account of the origins of this entropy change accompanying deformation.

Meyer, von Susich, and Valkó (27) in 1932 suggested that the decrease of entropy with elongation is a consequence of orientation of the molecular chains of which rubber is composed. Macroscopic elongation of the specimen requires

microscopic elongation of the irregular chains which comprise its structure, and an elongated chain represents a less probable (lower entropy) state than an irregular chain of random configuration. Thus, the retractive force is due chiefly to the tendency for the rubber structure to assume a more probable (disoriented) state, and does not arise from attractive forces of one sort or another within the structure.

At the present time the explanation of Meyer, von Susich, and Valkó for the change in entropy of rubber on stretching, and hence for the origin of the major component of the elastic retractive force, is almost universally accepted. The next problem, that of interrelating quantitatively the stress on the one hand with the strain and the network structure on the other, has been attacked by the methods of statistical mechanics. This involves evaluation of the available number of configurations (configurational "probability") as a function of deformation. The relative number of configurations can be converted to an entropy change by employing the Boltzmann relationship, and the stress can be computed from the resulting entropy function by straightforward methods of thermodynamics.

In this paper the various methods which have been advanced for treating the statistics of network deformation will be compared with one another and with experimental results. As an extension of these treatments of rubber elasticity, the effects of network imperfections, such as arise from the finite molecular weight of the unvulcanized rubber, will be incorporated into the theory. The connection between swelling of rubber vulcanizates in solvents and their elastic properties will be discussed.

II. NETWORK STRUCTURE OF VULCANIZED RUBBER

Before proceeding with a discussion of the various methods for dealing quantitatively with the statistics of rubber network deformations, it is necessary to consider briefly the structure of vulcanized rubber. Raw (unvulcanized) rubber consists of very long polymeric molecules, each composed of a thousand or more of the structural unit C_5H_8. In the unoriented (undeformed) state these thread-like molecules are randomly entangled in a completely haphazard manner. The configuration of any individual molecule resembles the path which would be traced by a molecule of a gas in travelling a distance equal to the length of the molecule, the mean free path of the gas molecule being equal to the length of one freely orienting segment of the polymer chain. From the point of view of structure, vulcanization consists of the introduction of intermolecular cross-linkages at randomly selected points of contact between molecules. These cross-linkages may occur on an average of once for every two hundred or so structural units in a soft gum vulcanizate. Thus, each molecule will be cross-linked to other molecules at an average of five or more points, and a continuous network structure will be developed. This network will extend throughout the piece of rubber. It will include very nearly all of the initial rubber molecules, inasmuch as the total number of cross-linkages considerably exceeds the total number of primary

molecules[2]. This is a consequence of statistical laws applied to random cross-linking processes (3, 4).

During the cross-linking process the rubber molecules lose their identities as individual units, being replaced by the continuous network structure mentioned above. The primary element of the network is the portion of a rubber molecule extending from one cross-linkage to the next one encountered along the molecule. This structural element will be referred to throughout this paper as a "chain."

Figure 1 represents an attempt to diagram a portion of the network structure, of necessity greatly oversimplified. The actual chains between cross-linkages will be much more irregular and will on the average meander through a considerably larger region of space extending beyond the junction points. Fur-
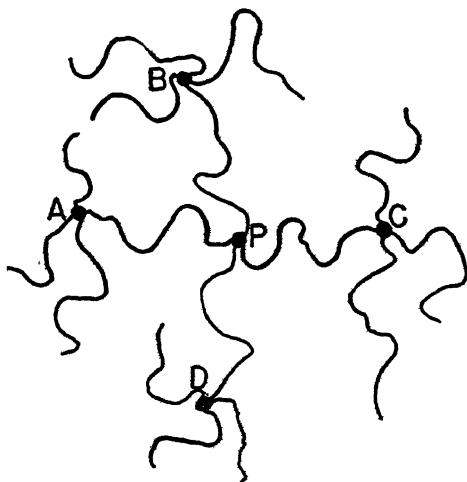
FIG. 1. Diagrammatic representation of a portion of the network structure surrounding the cross-linkage P.

thermore, other chains and cross-linkages, not immediately connected with those shown in the figure, will interpenetrate this same region of space.

The configurations of the chains in the undeformed piece of rubber will conform to the same description as has been applied to the unvulcanized molecule of raw rubber. Prior to cross-linking each chain exists as an element of a molecule, bound at either end to other similar elements. While its attachments to its neighbors hinder its *rate* of transformation from one configuration to another, they do not influence its *average* configurations. The chain configurations are completely random. Cross-linking does not disturb these configurations; it

[2] James and Guth (19) estimate that the proportion of vulcanized rubber which is actively combined with the network is small—about 25 per cent of the total. In addition to the fact that a numerical error occurs in their equations, their procedure is based on a hypothetical model for vulcanized rubber which bears little resemblance to the actual structure.

merely tends to fix them. Consequently, the configurations of the chains in undeformed vulcanized rubber are the same as would be assumed by a set of totally independent molecules of the same lengths as the chains.

The cross-linkages represent fixed points in the network structure in the sense that at each of them four chains are permanently connected. A cross-linkage may "diffuse" over a limited region of the space through rearrangements in the configurations of the associated chains. The restraint imposed by a cross-linkage requires that these rearrangements of the associated chains occur in unison in order that the chain ends shall always meet a common point.

Mean positions in space may be assigned to each cross-linkage. When the network is deformed these mean positions will be shifted like minute inclusions in a homogeneous isotropic medium. Thus, an elongation in the z direction with an increase in the length by the factor α will increase the z coördinate of the mean position of junction A with respect to that of P by the factor α. Coördinates in the perpendicular directions, the volume remaining constant, will be decreased by the factor $1/\sqrt{\alpha}$. The deformation produces a change in the distribution of chain "displacement lengths," or distances between chain ends. The result is an increase in the average chain displacement length. Consequently, there is a decrease in the number of configurations available to the system of interconnected chains—in other words, a decrease in the configuration probability. Various methods for arriving at a quantitative estimate of this entropy change will be discussed in the next section.

III. QUANTITATIVE TREATMENT OF RUBBER ELASTICITY

1. The chain length probability distribution

The common basis for all of the various statistical-mechanical derivations of stress–strain relationships for rubber and rubber-like substances is the equation expressing the probability distribution of chain displacement lengths for chains of random configuration. Taking one end of the chain as origin of coördinates, the probability that the other end lies within a volume element located at x, y, z, is expressed as (13, 23):

$$W(x, y, z)\, dxdydz = (\beta^3/\pi^{3/2}) \exp\left[-\beta^2(x^2 + y^2 + z^2)\right] dxdydz \qquad (1)$$

where the parameter β depends on the length of the chain and its flexibility. The nature of this dependence of β on chain structure is of no consequence in the development of elasticity theory; only the form of equation 1 is important. According to equation 1 the root mean square value of the chain displacement length $r(= \sqrt{x^2 + y^2 + z^2})$ must equal $\sqrt{3/2\beta^2}$.

No rigorous proof of the validity of equation 1 as applied to polymer molecules which derive their flexibility from permissible rotations about valence bonds of the chain has been given. However, for the case of "idealized" chains composed of many units joined by bonds at fixed angles about which there is free rotation, each unit possessing length but an inappreciable cross section ("volumeless" chains), the equation seems to be reasonably well founded (13, 23).

Lord Rayleigh's (32) analyses of an analogous problem, that of random flight in three dimensions, provides further support. Kuhn (6, 25) has shown that limitations on free rotation about bonds may be expected to alter β (for chains of given contour length) but not the form of equation 1.

Neglect of the volume occupied by the chain introduces a more dubious approximation. In effect, this approximation fails to exclude from consideration those configurations in which two (or more) units, separated some distance along the chain, would occupy the same element of volume. No quantitative treatment of the effect of this approximation has been carried out. It may be presumed, however, that proper exclusion of these impossible configurations would alter somewhat the character of the distribution.

Mention should also be made of the necessary deviation from equation 1 for large values of r, i.e., for r values approaching that for the fully extended chain. The actual distribution should halt at this limit, instead of approaching zero asymptotically as prescribed by equation 1. James and Guth (19, 20) have discussed this limitation at length, with the conclusion that at elongations above 300 per cent of the initial length the chains in representative vulcanizates are sufficiently extended to justify consideration of this correction. This is about the point at which crystallization sets in in natural rubber. Synthetic rubber pure gum vulcanizates either undergo crystallization at this or slightly higher elongations, or, lacking the ability to withstand the stress which develops, they are ruptured at about this point. Since the statistical treatment of elasticity becomes inapplicable quantitatively when crystallization occurs, it is doubtful that this correction is of any great practical importance.

In this paper we shall employ equation 1 as a reasonable approximation to the correct chain-length distribution function, realizing that it is neither rigorously proved nor quantitatively exact. To the extent that it expresses accurately the probability that a free molecule or chain will possess a displacement length r, it must also represent the relative number of configurations available to the chain for a fixed displacement length r, since the probability of a given state is proportional to the number of configurations consistent with that state. The function W will be referred to interchangeably as an expression for the probability of a given r value and for the relative number of configurations of a chain having the displacement length r.

2. The elastic characteristics of a single chain

We consider a single chain, one end of which is constrained to lie in a volume element about the point located at x, y, z with respect to the other end. Thus, the chain displacement length is fixed, but intervening portions of the chain are free to assume any configuration consistent with bond angles, steric interferences, etc. The configurational entropy of the single chain is given by the log of the number of configurations multiplied by Boltzmann's constant k. Hence, employing equation 1 for the relative number of configurations, there is obtained for the configurational entropy of a single chain, omitting an additive constant,

$$s = k \ln W = k[A - \beta^2(x^2 + y^2 + z^2)] \tag{2}$$

where A is a constant.[3] The maximum entropy occurs when

$$r = \sqrt{x^2 + y^2 + z^2} = 0$$

The force of retraction arising from the entropy change is

$$-T(\partial s/\partial r) = 2kT\beta^2 r \tag{3}$$

i.e., the chain is a Hooke's law spring, the tension in which is directly proportional to its length.

On the basis of this result James and Guth (14, 19, 20) replace the actual network of interconnected chains with a hypothetical "network" composed of three sets of parallel springs running the full length, breadth, and thickness of the piece of rubber. This hypothetical set of springs, it is shown, should reproduce the elastic properties of rubber. After taking into account the effects of an "internal pressure" on elastic properties at fixed volume, the following expression is obtained for the retractive force as a function of the degree of extension α:

$$f = 2mkT\beta^2[\alpha - 1/\alpha^2] \tag{4}$$

The number of parallel chains per unit cross-sectional area of James and Guth's system of springs is represented by m.[4] The dependence of f on α is precisely that found by other methods which treat the statistical mechanics of the actual rubber network. However, the coefficient m, expressing the number of chains *per unit area* of the hypothetical "parallel chain" model, is a fiction in terms of the actual network of irregular chains. The real chains occupy *volume*, not an area. Furthermore, equation 4 is dimensionally incorrect, f being expressed in force per unit volume. (β has the dimensions of reciprocal length.)

In conclusion, this procedure yields a satisfactory form for the dependence of stress on strain (α), but it fails to connect elastic properties with network structure.[5] Thus, the important relationship obtained by other methods (*cf. seq.*) between the elastic force of retraction and the number of chains per unit volume, or the directly related concentration of cross-linkages, is obliterated by the replacement of the network by sets of parallel chains.

3. Statistical mechanics of the network as a whole

A simpler and more satisfactory analysis of the elasticity problem can be carried out by considering the statistical mechanics of the network as a whole,

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[3] It may be objected that application of the methods of statistical mechanics, and of thermodynamics as well, to a system composed of only 10^2 to 10^3 units is unsound. While in the above we deal with a single chain, the actual results are to be applied to a system of many chains—some 10^{18} per cubic centimeter. Hence, we are concerned only with the average characteristics of a single chain.

[4] Substituting $\beta^2 = 3/2 \bar{r}^2$ in equation 4 yields an expression differing from James and Guth's equation 3.3 of reference 19 by a factor of three, omitted from their equation (their L replaces our r). In an earlier publication (14) the coefficient is correctly expressed as in equation 4 above.

[5] This is in agreement with a conclusion drawn by James and Guth in a comparison of their method with others. See page 377 of reference 19.

without regard for the so-called elasticity of a single chain. This is the method applied by Kuhn (24), Wall (37), and Treloar (35).

The internal state of the network system can be specified in terms of the positions of the cross-linkages. As pointed out earlier, deformation of the rubber transforms the arrangement of these points, and hence alters the internal state of the network. Any such state can be represented by the system of vectors connecting neighboring junction points, i.e., the system of vectors each of which connects the two ends of a chain. If these displacement vectors are shifted to a common origin and the surrounding space is marked off into volume elements numbered 1, 2, 3, etc., the number of vectors terminating in the ith volume element can be designated by ν_i. The state of the system is defined by assigning a value to each of the ν_i, subject, of course, to the condition that $\Sigma \nu_i = \nu$, where ν is the total number of chains. Each chain may assume a number of configurations through rearrangement of intervening portions of the chain, its displacement vector remaining fixed. For chains having vectors terminating in the ith cell, the relative number W_i of these configurations is given by equation 1 with x, y, z corresponding to the coördinates of the ith cell.

The probability P of a given state is given by the product of the probabilities, or relative number of configurations, for each chain. Hence,

$$P = \prod_i (W_i)^{\nu_i} \tag{5}$$

This expression has been employed by Kuhn (24) and Treloar (35).[6] Wall (37) considers that the chains are interchangeable, and includes, therefore, a factor for the number of combinations of a total of ν vectors such that ν_1 of them terminate in cell "1," ν_2 in cell "2," etc. Instead of equation 5, Wall uses the equation

$$P = [\prod W_i^{\nu_i}][\nu!/\prod \nu_i!] \tag{5'}$$

The assumed interchangeability of chains is inconsistent with the mutual interdependence of the chains of the network. However, the second factor in brackets in equation 5' is of no consequence in deformations unaccompanied by a change in volume. In all such cases this factor remains unchanged, and therefore does not affect the final results.

Taking the logarithm of equation 5 and multiplying by the Boltzmann constant to obtain the entropy:

$$S = k \sum_i \nu_i \ln W_i = k \sum_i \nu_i [A - \beta^2(x_i^2 + y_i^2 + z_i^2)] \tag{6}$$

[6] Kuhn (24) failed to recognize that the restraints imposed on a chain are limited to its ends, the intervening portions being free to assume whatever configuration is consistent with the given chain displacement length. In his analysis he introduced additional restraints on the mid portion of the chain. Treloar (35) has corrected this error in Kuhn's treatment and has presented an exact solution of the resulting equations instead of the approximate solution limited to very low elongations submitted by Kuhn.

In the undeformed state the distribution of chain displacement lengths will be that given by equation 1, the cross-linkages having been introduced at random between unoriented chains. Then

$$\nu_i = \nu W_i \, dx dy dz$$

If the sample is elongated in the z direction, the length being increased by the factor α, then, under the assumption that the relative positions of the network junctions change in accordance with the macroscopic dimensions of the sample, the z coördinate of each vector will be increased by the factor α and x and y will be decreased by $1/\alpha^{1/2}$, the volume remaining constant. A chain for which the projected distance between its ends is equal to z possessed a component equal to z/α before stretching. Hence to obtain the new distribution of chain lengths after stretching, z in equation 1 must be replaced by z/α. Similarly, x and y must be replaced by $x\alpha^{1/2}$ and $y\alpha^{1/2}$. In place of equation 1 we have, therefore,

$$W'(x, y, z) \, dx dy dz = (\beta^3/\pi^{3/2}) \exp\left[-\beta^2(\alpha x^2 + \alpha y^2 + z^2/\alpha^2)\right] dx dy dz \qquad (1')$$

Substituting $\nu_i = \nu W'_i \, dx dy dz$ in equation 6 and replacing the summation by integrals:

$$S = k\nu(\beta^3/\pi^{3/2}) \int\!\!\!\int\!\!\!\int_{-\infty}^{+\infty} \exp\left[-\beta^2(\alpha x^2 + \alpha y^2 + z^2/\alpha^2)\right][A - \beta^2(x^2 + y^2 + z^2)] dx dy dz$$

Treloar (35) has integrated this expression, obtaining a result which becomes, when expressed as the entropy change in passing from the undeformed state $\alpha = 1$ to the deformed state defined by α:

$$\Delta S = S(\alpha) - S(1) = -k\nu(\alpha^2 + 2/\alpha - 3)/2 \qquad (7)$$

This expression was obtained previously by Wall (37), employing equation 5' and a different mathematical procedure.[7] The entropy contribution to the elastic retractive force may be computed at once from Wall's equation (equation 7)

$$f = -T(\partial S/\partial L) = -T(\partial S/\partial \alpha)/L_0 = (kT\nu/L_0)(\alpha - 1/\alpha^2) \qquad (8)$$

where L_0 is the initial length of the unstretched sample. This equation, relating the elastic retractive force to network structure as represented by ν and to the deformation α, was first obtained by Wall. The tension τ (force per unit initial cross-sectional area) is given by either of the alternate expressions

$$\tau = RT(\nu/V)\varphi(\alpha) \qquad (9)$$

or

$$\tau = (RT\rho/M_c)\varphi(\alpha) \qquad (9')$$

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[7] In deriving equation 7 all chains have been assumed to be of the same size, i.e., the same contour length. Considering the random nature of vulcanization this obviously is far from fact. For a system of heterogeneous chains, this same procedure may be applied to each set of chains of a given size. The final result summed over all sizes of chains is precisely equation 7, where ν is the total number of chains of all sizes.

where ν is the number of chains in the volume V, M_c is the molecular weight per chain (number average), ρ is the density of the rubber, and

$$\varphi(\alpha) = \alpha - 1/\alpha^2 \qquad (10)$$

Whereas the previous equation (4) contains the $\varphi(\alpha)$ function, the dependence of the coefficient on the number of chains, or on the concentration of cross-linkages, does not occur therein. The simple connection between the elastic "modulus" and network structure provided by equations 8, 9, or 9' is of the utmost importance.

4. The tetrahedral model for the network structure of rubber

An alternative procedure (7) for statistical treatment of rubber network deformations can be carried out in terms of an average "cell" of the network.[8] Instead of considering the chains as individual elements, the four chains meeting at a junction are considered mutually. The four chains radiating from each junction lead to four "nearest neighbor" junctions, the average positions of which define a tetrahedron. One such tetrahedron is defined by the points A, B, C, and D in figure 1, considered in three dimensions. If we idealize the network to the extent of making all chains of the same size (same contour length), then the *average* tetrahedron, or "cell," so defined will be a *regular* tetrahedron. It should be made clear at the outset that, owing to the intertwining of the chains, these tetrahedral cells will overlap extensively, a given element of the volume being encompassed by many of these elementary tetrahedra. These cells do not adjoin one another with the regularity and volume-filling character of the unit cells of a diamond lattice, for example.

The tetrahedral cell is represented diagrammatically in figure 2. The existence of this cell as a unit of the network structure rests entirely upon the requirement that four chains extending from the corners (A, B, C, and D) shall meet within a volume element $\Delta\tau$ at some point P. The relative number of configurations available to the system of four chains which meet within a *particular* volume element $\Delta\tau$ is given by the product of four "probabilities" for the individual chains

$$P(\Delta\tau)^4 = \prod_{i=1}^{4} [W(x_i y_i z_i)\Delta\tau_i]$$

where x_i, y_i, z_i, etc. are the coördinates of the same volume element $\Delta\tau$ referred, respectively, to the four corners of the tetrahedron A, B, C, and D. Substituting from equation 1 and integrating over the space in order to obtain the relative number of configurations when the chains meet in the same volume element located *any place*:

$$P(\Delta\tau)^3 = (\beta^{12}/\pi^6) \left[\int_\tau \exp\left(-\beta^2 \sum_{i=1}^{4} r_i^2\right) \Delta\tau \right] (\Delta\tau)^3 \qquad (11)$$

[8] The derivation given here is a simplification of the more rigorous treatment by Flory and Rehner (6, 7).

It can be shown from the geometry of the tetrahedron that

$$\sum_{i=1} r_i^2 = 4a^2 + 4\lambda^2(\alpha^2 + 2/\alpha)/3$$

where a is the radial distance of P from the center O of the tetrahedron, λ is the distance from O to one of the corners of the undeformed tetrahedron, and α is the relative elongation of the tetrahedron resulting from deformation of the piece of rubber without change in volume. The average tetrahedron is assumed
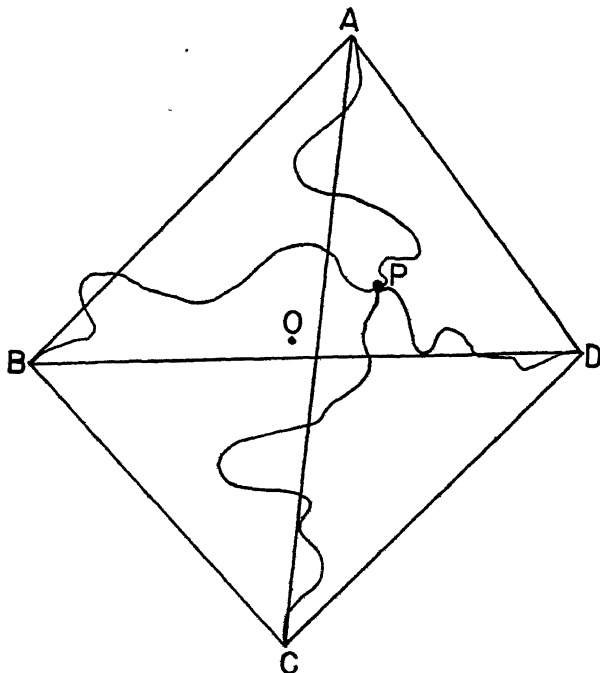
Fig. 2. Unit tetrahedral "cell" surrounding the central junction P

to be deformed in proportion to the changes in macroscopic dimensions. Substituting in equation 11:

$$P = (4\beta^{12}/\pi^5) \int_0^\infty \exp\left[-4\beta^2 a^2 - 4\beta^2\lambda^2(\alpha^2 + 2/\alpha)/3\right]a^2 \, da \qquad (12)$$

The relative configurational probability for the stretched and normal states is obtained by dividing $P(\alpha)$ by $P(1)$. Dividing equation 12 by its value for $\alpha = 1$, the relative configurational probability of the stretched rubber becomes

$$P(\alpha)/P(1) = \exp\left[-4\beta^2\lambda^2(\alpha^2 + 2/\alpha - 3)/3\right] \qquad (13)$$

The distance λ from the center to a corner of the undeformed tetrahedron may be taken equal to the root mean square chain displacement length (r) which, according to equation 1, is equal to $\sqrt{3/2\beta^2}$. Then, taking the logarithm of

equation 13 and multiplying by Boltzmann's constant, the entropy of deformation becomes

$$\Delta s = -2k(\alpha^2 + 2/\alpha - 3)$$

for the tetrahedral cell. Since each cell contains four chains, multiplication by $\nu/4$ should give the entropy change for the network as a whole. The result is identical with Wall's equation (equation 7), from which the elasticity equations (8 and 9) are derived by standard procedures of thermodynamics.

IV. COMPARISON OF THE THEORY WITH EXPERIMENTAL RESULTS

In the preceding section it has been shown that the various statistical-mechanical treatments of rubber elasticity agree on the form of the force–elongation relationship for vulcanized rubber as represented by equation 10. Isothermal stress–strain curves for rubber (1, 16, 26, 36), synthetic rubber (31), and rubber-like polymers (29) are reasonably well reproduced by this function at elongations preceding the onset of crystallization. The experimentally determined contribution to the retractive force of the change in heat content on stretching is very small compared with the total tension. This term, which has been neglected in the above theory, does not alter the force–elongation curve significantly below the region of crystallization (1, 36). Treloar has shown that measurements on natural rubber in compression ($\alpha < 1$) are in excellent agreement with equation 10.

It is significant that the form of the dependence on α (i.e., $\varphi(\alpha)$) is unaffected by the degree of cross-linking. Stress–strain curves for different degrees of vulcanization, therefore, should be superimposable by altering the stress scale by suitable factors. This prediction finds verification for natural rubber (16) and Butyl rubber (10) vulcanizates differing in degree of cure. Hence a single quantity, the stress at a given elongation, will suffice to characterize the stress–strain curve as a function of the degree of vulcanization, except at higher elongations where crystallization sets in.

The connection between elastic properties and vulcanizate structure is of more far-reaching importance than the exact form of the stress–strain curve. Wall's equation (9), which is substantiated by Treloar's modification of Kuhn's treatment and by the method of Flory and Rehner, furnishes an explicit expression for the constant of proportionality between $\varphi(\alpha)$ and the absolute tension. This proportionality constant contains the number of chains, ν, which for an ideal network formed from indefinitely long primary molecules must equal twice the number of cross-linkages. Thus, the tension at any given elongation is predicted to be proportional to the degree of cross-linking of the molecules.

The degree of cross-linking in a vulcanizate is not easily determined directly. Prior to a recent investigation (10) of the physical properties and structure of Butyl rubber, no comparison between the tension at a given elongation and the independently estimated degree of cross-linking in a vulcanized rubber was available. Butyl rubber, a copolymer of isobutylene with a small percentage of a diolefin, provides an ideal case for such a test, inasmuch as the cross-linking

capacity can be controlled through the diolefin content of the polymer. The concentration of cross-linkages formed in the vulcanization (fixed recipe) of Butyl polymers of a given diolefin content was determined as follows: Raw polymers were separated by fractionation into a series of samples of comparatively narrow molecular weight range, each of which possessed the same percentage of unsaturated (diolefin) units and, hence, the same cross-linking capacity. Each of these was compounded and cured under standardized conditions; thus were produced in each sample the same number of cross-linkages per unit amount of polymer. The vulcanizates were extracted with cyclohexane at room temperature to remove soluble constituents. These are negligible for fractions of
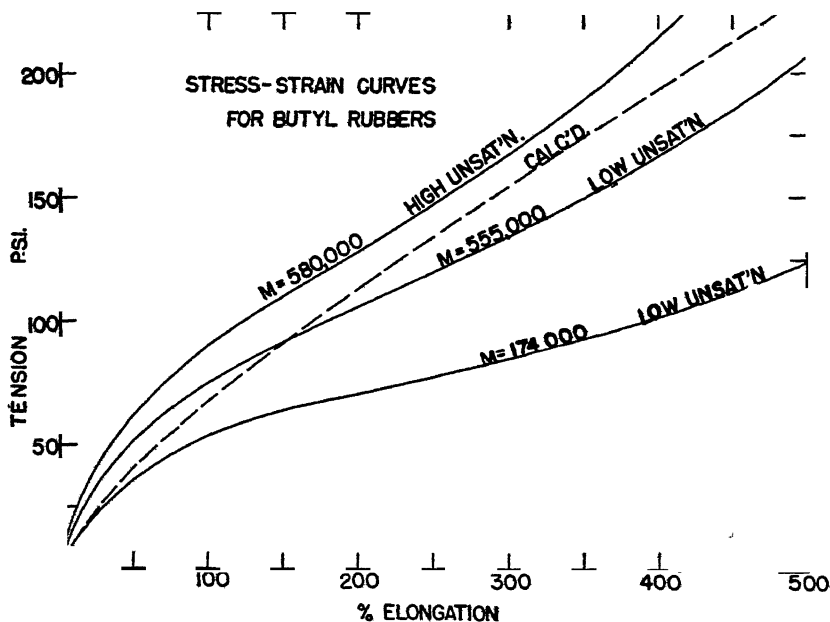
FIG. 3. Stress–strain curves for several pure gum vulcanizates from fractionated Butyl rubber polymers. Molecular weights are indicated. The calculated curve represents $\varphi(\alpha)$ as given by equation 10.

high molecular weight, where each molecule on the average enters into a number of cross-linkages. As the molecular weight is decreased the percentage of "sol" eventually increases rapidly, reaching 100 per cent at the "gel point" or critical molecular weight M' for incipient insolubility. This critical molecular weight was estimated by an extrapolation of the percentage of sol plotted against molecular weight of the fraction.

From the theory of random cross-linking (3, 4, 34) it is known that for molecules of uniform length incipient gelation occurs when the number of cross-linkages equals half the number of initial molecules. Hence, the concentration of cross-linkages in moles per gram is equal to $1/2M'$ throughout the entire series of vulcanizates from polymers of the same cross-linking capacity. Recall-

ing that in a network formed from indefinitely long molecules the number of chains is twice the number of cross-linkages, it is evident that M_c equals M', the critical molecular weight for incipient gelation at fixed cross-linking capacity.

Several stress–strain curves for Butyl rubber vulcanizates prepared from fractionated samples differing in molecular weight and in unsaturation are shown in figure 3. The values for M_c, estimated as outlined above, are 35,000 and 20,000, respectively, for the vulcanizates from the low and high unsaturation samples. The tensions at 300 per cent elongation for the high-molecular-weight rubbers, 108 and 134 pounds per square inch, respectively, are greater than the values, 38 and 66 pounds per square inch, calculated from the M_c's using equation 9'. In addition to the discrepancy in magnitudes, the change in "modulus" with the degree of cross-linking is less than a direct proportionality predicted by theory. Furthermore, the dependence on molecular weight is rather large.

Correlation between the above theory and experimental results on the stress–strain properties of rubber and rubber-like materials may be summarized as follows: The statistical theory of rubber elasticity predicts a form for the stress–strain curve which is in good agreement with experiment. The effect of change in heat content with elongation is small. On the other hand, the magnitude of the observed tension at a given elongation is somewhat larger than the above theory predicts, at least in the case of Butyl rubber. The tension varies less rapidly with the concentration of cross-linkages than the predicted direct proportionality. The large observed dependence on the initial molecular weight of the unvulcanized polymer is nowhere taken into account in the above theory. Further refinements of the theory discussed in the next section provide explanations for these deviations.

V. NETWORK DEFECTS: THE INFLUENCE OF MOLECULAR WEIGHT ON ELASTIC PROPERTIES

The various derivations of the basic equations 9 and 9' stem from the same physical concepts of network structure. In attempting refinements which will remove the discrepancies between theory and experiment pointed out above, it will be necessary therefore to reconsider this structure in greater detail.

1. Network entanglements

The fact that the elastic force of retraction in Butyl rubber vulcanizates exceeds the value calculated from equation 9, in which $\nu/2$ is identified as the number of chemical cross-linkages, suggests that types of chain interactions other than primary valence attachments between chains are to be reckoned with. Several possibilities require consideration.

Attachments between chains due to van der Waals forces have been postulated as a source of cross-linkages in rubber-like materials. There is no doubt as to the existence of such forces between polymer molecules. The question of concern here is the permanence with which these forces may unite neighboring chains. In order for such an attachment to function as a network cross-linkage, obviously it must endure at least over the interval of the elasticity measurement. On the

other hand, the existence of the rubbery state in any high polymer predicates
a high degree of internal mobility which will allow elements of the chains to slip
past one another during deformation.   van der Waals attractions between chains
must be small in order for the material to be rubber-like.

In harmony with this deduction rubber-like materials usually possess non-
polar (hydrocarbon) chains or, if they contain strong polar groups, rubber-like
character is exhibited only at elevated temperatures or in the presence of a
solvent or plasticizing substance capable of satisfying the forces of the polar
groups.   The probable existence of occasional strong polar, or possibly ionic,
interchain bonds in certain rubbery materials cannot be denied, e.g., in aqueous
protein gels and possibly to a very limited extent in raw, unmasticated natural
rubber containing traces of polar substituents (30).   The occurrence of a signi-
ficant number of such bonds in vulcanized natural rubber or in hydrocarbon
synthetic rubbers is exceedingly unlikely in view of their non-polar nature and
the consequent weak van der Waals forces between chains.   If such bonds
contributed to the elastic properties, their number should decrease with tempera-
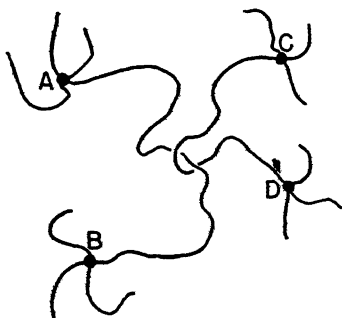
FIG. 4. Entanglement of chains within the network structure

ture and the elastic retractive force should show a corresponding diminution,
which is contrary to observation.   Furthermore, the correlation of swelling
behavior of Butyl vulcanizates with elastic properties (cf. seq.) demonstrates
that about as many cross-linkages are operative in the presence of solvent as
in its absence.   van der Waals bonds would be expected to be eliminated, or at
least diminished in number, in the presence of a solvent.

It has been suggested (12) that long chains, merely owing to their irregular
configurations, become entangled with one another to the extent that a molecule
is unable to extricate itself from its neighbors.   Two arguments, one theoretical
and the other based on direct experiments, can be leveled against the view that
these entanglements of linear (non-network) molecules are equivalent in their
contribution to elasticity to permanent, or primary valence, cross-linkages.
Investigations of electrical (11) and viscous (2, 21) properties of polymers in the
rubber-like or liquid state reveal that within each chain small elements, or seg-
ments, composed of perhaps ten or twenty chain atoms are constantly rear-
ranging their positions at a rapid rate under the influence of thermal agitation.
Successive random rearrangements of these segments lead to diffusion not only

of the segments but of the molecule as a whole from one configuration and position to another. Hence, a molecule does not maintain fixed relationships with respect to its neighbors. Although entanglement of linear molecules is a factor contributing to resistance to flow (high viscosity) and to a low *rate* of solution, it should not be expected to eliminate plastic flow or to affect *equilibrium* solubility. These contentions are confirmed by experimental results: All linear polymers regardless of molecular weight display the properties of unvulcanized rubber above their brittle point temperatures, i.e., they are soluble in suitable solvents and under stress they undergo plastic flow at a non-diminishing rate.

The situation is otherwise if there exists a primary valence network structure. Here entanglements of chains may lead to restraints which are equivalent to additional chemical cross bonds in their contribution to network properties. Consider, for example, two chains, one looped about the other, such as are shown in figure 4. While the chains AB and CD are not bound together at fixed points as in a chemical cross-linkage, they nevertheless are permanently prevented from crossing each other. The configurations available to each chain
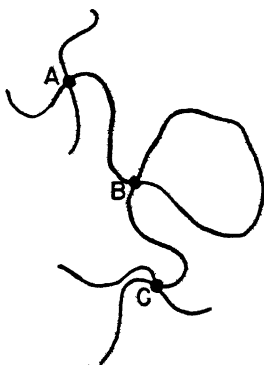
FIG. 5. Intramolecular cross-linking

are limited by interference with the other. This type of restraint, which will be called a network entanglement, is of a permanent nature; it cannot be circumvented without disrupting a portion of the primary valence network. One of these entanglements may not be quantitatively equivalent to a chemical cross bond in its contribution to elastic properties. However, a number of them along each chain may raise the effective number of cross-linkages appreciably above the actual number.

It should be reëmphasized that these network entanglements would offer no permanent barriers to chain configuration were it not for the chemical cross bonds which are responsible for the primary valence network structure. Their existence as permanent features of the structure is dependent upon the presence of primary valence cross-linkages.

2. Intramolecular cross-linkages

Occasionally two parts of the same molecule may become cross-linked, thus forming a loop as shown in figure 5. If there are no other intervening cross-

linkages with other chains along the loop, then configurations of the loop will be unaffected by deformations. This portion of the structure can contribute no reaction to deformation. The entire portion between the cross-linkages A and C will act as a single chain, and the cross-linkage B is wasted. Cross-linkages of this type should be deducted from the total number in obtaining the number of effective cross-linkages. Estimates of the number of such intramolecular cross-linkages for flexible chains of random configuration indicate that they constitute only a few per cent of the total. Their further consideration is scarcely warranted at the present time.

3. Terminal chains: the effect of initial molecular weight

Previous treatments (7, 14, 19, 20, 35, 37) of rubber elasticity have disregarded the influence on network structure and properties of the molecular weight of the initial rubber molecules from which the network is formed by vulcanization. In other words, the molecules were assumed to be infinitely long. Experiments already have been quoted which emphasize the marked dependence of elastic properties on initial molecular weight of the raw rubber. These are supported

(a)   (b)
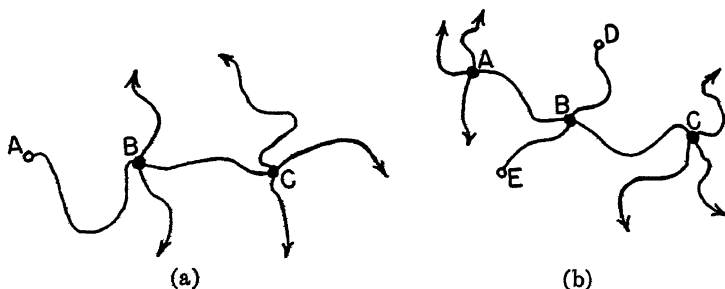
FIG. 6. The effect of ends of molecules on network structure: ● indicates a cross-linkage, ○ the terminus of a molecule, and → signifies continuation of the network structure.

by widespread experience in rubber technology. The reason for this dependence is found in the fact that each end of an initial molecule contributes a flaw to the final network structure. The portion of a molecule from one end to its first cross-linkage along its length, as depicted in figure 6a, contributes nothing to the response of the network to deformation. The chain AB is always free to assume any configuration whatever, owing to the freedom of the end A. Similarly, attachment of the network at the point B in figure 6b, to a molecule such as DE which is bound to the network at no other point produces no increase in the effective number of chains. Not only are the two chains DB and BE of molecule DE inactive, but the cross-linkage at B is not a point of constraint on the chain AC. Hence, the portion of the network from A to C is to be considered as a single chain, as if the cross-linkage at B were not present.

This discussion of imperfections in networks of finite chains might be extended to more complex situations. However, the above should be sufficient to demonstrate qualitatively the manner in which finite molecule length will affect the

network structure. Quantitative derivation of the effect of molecule length on network properties can best be accomplished by assuming a different approach.

We consider the process of network formation by successive cross-linking of molecules. Let it be supposed that cross-linking is allowed to occur only between molecules, or cross-linked combinations of molecules, which have not been connected directly or indirectly by previously introduced cross-linkages. When there are a total of $N - 1$ cross-linkages connecting N primary molecules "intermolecularly,"[9] all molecules will be bound to a single ramified structure. Before allowing the cross-linking process to continue further, let us consider the properties of the macrostructure developed at this stage. It would be incorrect to call it a network, inasmuch as it contains no net-like structure, i.e., it possesses no circuitous connections within its structure. Because of this fact one portion of the structure can be shifted to a new position or configuration without affecting permanently the configurations of other parts. So far as their average configurations (as apart from their positions in space) are concerned, the various elements of the structure are independent of one another. Likewise, macroscopic deformation does not impose permanent restraints on the configurations of component portions of the structure. This somewhat hypothetical structure should be expected to display a static modulus of elasticity equal to zero.

Additional cross-linking necessarily will be "intramolecular." Closed circuits of interconnected molecules will be produced, and the structure can then properly be referred to as a network. It becomes apparent that it is these circuitous paths in the network which are effective in transmitting the effects of changes of configuration of one part of the structure to another part. Macroscopic deformation can no longer occur without a change in internal configuration which cannot be dissipated through chain rearrangements, barring primary valence rupture. A little consideration will show that for each additional network cross-linkage one new closed circuit, and two active network chains, are formed. (It will be recalled that the number of chains in an ideal network formed from "infinitely" long molecules is twice the number of cross-linkages.)

In the course of the actual formation of the network, intermolecular and intramolecular cross-linking are not sharply differentiated. Nevertheless, the number of circuitous paths in the network, exclusive of non-network, or sol constituents, necessarily will be equal at any stage of the process to the total number of cross-linkages, $\nu_0/2$, in the network minus the number, $N - 1$, of cross-linkages required to combine the primary molecules into a single continuous structure without intraconnecting two parts of the structure to form closed circuits. Hence, the total number of circuitous paths in the network, or, alternatively, the total number of "intrastructural" cross-linkages, will be

$$\nu/2 = \nu_0/2 - N$$

[9] The term "intermolecular" cross-linkages is used in this and the succeeding paragraph to refer to cross links connecting previously separate molecular species. Each of these may be a cross-linked combination of "molecules" in the restricted sense of primary linear rubber molecules, as employed elsewhere in this paper.

wherein $N - 1$ is replaced by N. The effective number of chains will be given by twice this quantity, or

$$\nu = \nu_0(1 - 2N/\nu_0)$$
$$= \nu_0(1 - 2M_c/M) \tag{13}$$

By introducing this expression into equation 9 or 9', a revised relationship between elastic retractive force and network properties is obtained which takes into account the effects of finite length of the initial molecules. This equation may be written

$$\tau = (RT\nu_0/V)(1 - 2M_c/M)\varphi(\alpha) \tag{14}$$

Before discussing this equation further, two aspects of its application should be clarified. In the first place the manner in which the occurrence of network entanglements such as have been discussed above will require modification of equation 14 must be considered. Inasmuch as entanglements affect only the active chains of the network, and not the terminal inactive chains such as AB in figure 6a, their effect to a first approximation should be proportional to the number ν of active chains and not to ν_0. It will be necessary, therefore, to increase ν in equation 13 by a factor g. This factor probably will depend on M_c and perhaps on the character of the vulcanization (cf. seq.). The modified equation for the tension becomes

$$\tau = (RTg\nu_0/V)(1 - 2M_c/M)\varphi(\alpha) \tag{14'}$$

It is important to note that the factor which introduces the correction for the molecular weight M of the primary rubber molecules is unaffected; M_c refers to the average molecular weight between primary valence cross-linkages, unmodified by entanglements.

Secondly, the above method for computing the number of closed circuits in the network requires revision when the average number of cross-linkages attached to each molecule is small. Here an appreciable proportion of the material consists of a sol fraction which is unattached to the network structure. The proportion of sol is determined (3, 4) by the "cross-linking index" γ, which for primary molecules of uniform length is equal to ν_0/N, i.e., to twice the ratio of cross-linkages to primary molecules. Incipient network formation[10] occurs at $\gamma = 1$. As the number of cross-linkages is increased, the proportion of gel (network) increases rapidly toward an asymptotic 100 per cent. It is only the gel fraction which is responsible for elasticity. Hence, in employing equation 13, ν_0 and N should refer exclusively to the gel fraction. Equations have been derived previously (4) for obtaining the cross-linking index, γ'', for the gel and the percentage of gel from the cross-linking index, γ, of the material as a whole. ν_0 and N for the gel alone can then be computed and the revised expression for ν introduced in place of equation 13. Trial calculations of this sort show that above $\gamma \sim 3$, where the percentage of sol is small, no appreciable error results if ν_0 and N are allowed to refer to the total material without distinguishing sol

[10] For a system of molecules of non-uniform length, Stockmayer (34) has shown that γ should be taken as the *weight average* number of points of cross-linkages per molecule.

from gel.   Hence, so long as M is at least three times M_c, the second factor in equations 14 and 14′ requires no correction for the existence of a small fraction of inactive sol.

4. Comparison of revised equations with experimental results

In figure 7 the force of retraction at 300 per cent elongation ($\alpha = 4$) for a series of pure gum Butyl rubbers (10) vulcanized to the same degree of cross-linking (constant M_c) is plotted against the reciprocal of the molecular weight
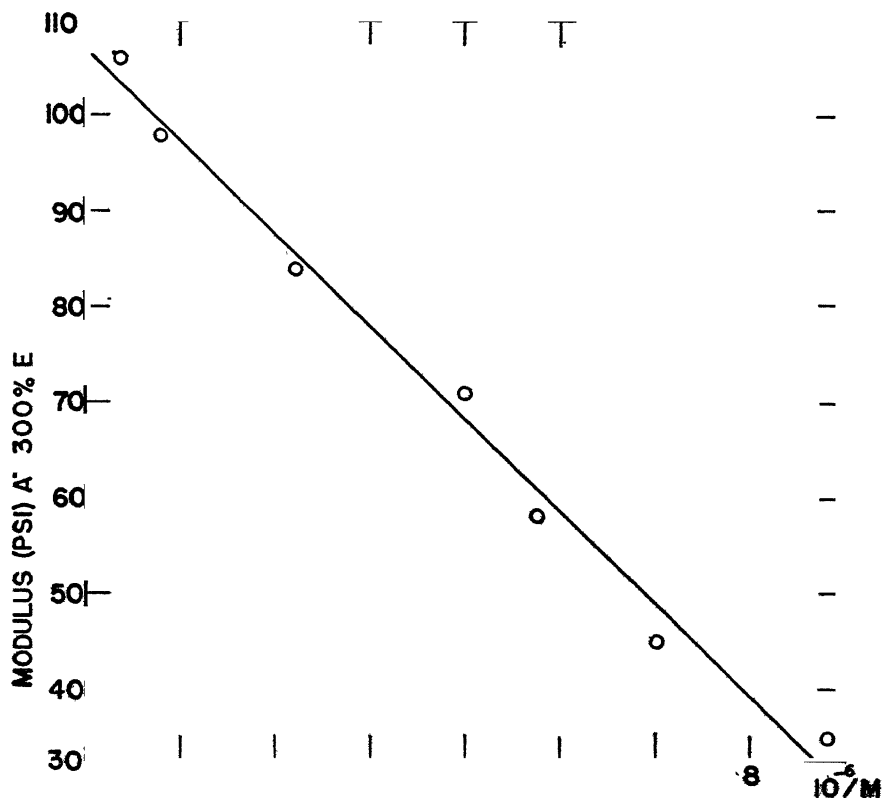
FIG. 7. Relationship between modulus and swelling.   Tension ("modulus") at 300 per cent elongation for a series of Butyl vulcanizates having the same concentration of cross-linkages, plotted against the reciprocal of the molecular weight of the polymer before vulcanization.

prior to vulcanization.   Fractionated polymers of relatively homogeneous molecular weight were used.   The plot is observed to be linear, in agreement with equations 14 and 14′, over the range $M = 114{,}000$ to $730{,}000$.   The equation of the straight line in pounds per square inch is

$$\tau_{300\%} = 127(1 - 77{,}000/M)$$

The indicated value of M_c is 38,500, in good agreement with the figure of 35,000 independently estimated as described earlier in this section.   Taking $M_c = 35{,}000$, the value of g in equation 14 calculated from the above coefficient is 3.3.

A similar series for which M_c was estimated to be 20,000 yielded an intercept at about 140 pounds per square inch, corresponding to $g = 2.1$.

The results shown in figure 7 furnish excellent confirmation for the second factor in equations 14 and 14' and for the explanation which has been given for the influence of molecular weight prior to vulcanization on elastic properties of the vulcanizate. The effects of entanglements in augmenting the elastic tension appear to be rather large. As the degree of cross-linking is increased, and M_c decreases correspondingly, the entanglement coefficient g decreases, presumably owing to the diminished number of entanglements per chain as the average length of the chains is reduced.

These rather large g factors may in part be due to a peculiarity of Butyl vulcanizates. In the vulcanization of this rubber there are only a limited number of points at which cross-linking may occur,—namely, at the diolefin units which are present only in relatively very small number. Furthermore, the process' probably is exhaustive; all diolefin units either enter into cross-linkages, or are permanently lost for this purpose owing to side reactions in the sulfur vulcanization process (10). In order for the rarely occurring unsaturated units to meet in juxtaposition, some extreme configurations probably are required. In these the degree of entanglement may be much greater than would occur in a more highly unsaturated rubber in which vulcanization is possible at almost any point where two chains meet.

VI. THE RELATIONSHIP BETWEEN SWELLING CAPACITY OF RUBBER VULCANIZATES AND ELASTIC PROPERTIES

1. Theory

In contrast to plastic raw rubber, vulcanized rubber swells without dissolving when placed in a solvent. This swelling process continues until an equilibrium state is reached, at which the volume of the swollen gel may exceed the initial volume of dry rubber five- to ten-fold (33, 38). Swelling of the rubber involves a distortion of the network structure not unlike that accompanying stretching, except that swelling is isotropic in three dimensions. Swelling equilibrium represents a balance between two opposing tendencies: the ordinary gain in entropy resulting from mixing of the two substances, and the decrease in entropy due to distortion (expansion) of the network. Since the forces associated with the latter change originate from the same source as the elastic retractive force, it is not surprising that elastic properties and swelling capacity are closely related (22, 33).

A detailed analysis of the thermodynamics of swelling has been carried out by Flory and Rehner (6, 8), employing the tetrahedral model for network structure previously discussed. Here a simpler treatment parallelling the Kuhn–Treloar procedure for elastic deformation will be given.

The partial molal free energy of dilution of polymer with solvent has been shown by Huggins (17) and the writer (5) to be given by

$$\Delta \bar{F}_{m,1} = RT[\ln (1 - v_2) + v_2 + \mu v_2^2]$$ (15)

where v_2 is the volume fraction of polymer and μ is a parameter which contains a heat of mixing term (temperature dependent) and an empirical constant the origins of which are not altogether clear (9). For present purposes it will suffice to consider μ as a parameter characteristic of any given liquid pair (18),—solvent and polymer.

The expansion of the network which accompanies absorption of solvent produces a decrease in configurational entropy of the network, an expression for which can be derived by a procedure paralleling the derivation of equation 7 for the change in entropy on stretching. The relative volume increase (ratio of volume of swollen gel to volume of dry rubber) is equal to $1/v_2$. For isotropic swelling, each linear dimension will increase by the factor $1/v_2^{1/3}$. Following the Kuhn-Wall-Treloar procedure, we again assume that the relative positions of the network junctions change in proportion to the macroscopic dimensions. By analogy with equation 1', the distribution of chain displacement lengths in the swollen "gel" is expressed by

$$W''(r)\,dr = (4\beta^3/\pi^{1/2})\,\exp\,(-\beta^2 r^2 v_2^{2/3})v_2 r^2 dr \tag{1''}$$

where $x^2 + y^2 + z^2$ has been replaced by r^2. Substituting $\nu_i = \nu W''_i\,dr$ in equation 6, the configurational entropy of the swollen network becomes

$$S = (4k\nu\beta^3/\pi^{1/2}) \int_0^\infty [\exp\,(-\beta^2 r^2 v_2^{2/3})][A - \beta^2 r^2]v_2 r^2\,dr$$

Integrating and subtracting S for $v_2 = 1$, the network entropy change due to swelling is given by the equation

$$\Delta S_e = -(3k\nu/2)(1/v_2^{2/3} - 1) \tag{16}$$

Aside from whatever heat of interaction between solvent and polymer may accompany the absorption of solvent (and this has already been included in μ of equation 15), the expansion of the network involves no change in internal energy; it is purely a configurational change. Hence, the free energy of expansion of the network is given by the alternate expressions

$$\Delta F_e = (3kT\nu/2)(1/u_2^{2/3} - 1)$$
$$= (3kT\nu/2)\{[Z\nu + n)/Z\nu]^{2/3} - 1\} \tag{17}$$

where v_2 has been replaced by its equivalent $Z\nu/(Z\nu + n)$, where n is the number of solvent molecules, ν is the number of chains, and Z is the ratio of the average size (volume) of a chain to the size of a molecule of solvent. Differentiating equation 17 with respect to n, the contribution to the partial molal free energy due to the reaction of the network to swelling is found to be

$$\Delta \bar{F}_{e,1} = (RT/Z)[Z\nu/(Z\nu + n)]^{1/3} = RT v_2^{1/3}/Z$$

Replacing Z by $M_c/\rho V_1$, where V_1 is the molar volume of the solvent and ρ is the density of the undiluted rubber:

$$\Delta \bar{F}_{e,1} = (RT\rho V_1/M_c)v_2^{1/3} \tag{18}$$

The partial molal free energy change, due both to mixing of the chains with solvent and to expansion of the network, is given by

$$\Delta \bar{F}_1 = \Delta \bar{F}_{m,1} + \Delta \bar{F}_{e,1}$$
$$= RT[\ln (1 - v_2) + v_2 + \mu v_2^2 + (\rho V_1/M_c)v_2^{1/3}] \quad (19)$$

Although this equation has other applications (8), we shall be concerned here only with equilibrium swelling, which is so closely related to elastic properties. At equilibrium with excess pure solvent $\Delta \bar{F}_1 = 0$. From equation 19

$$M_c = -\rho V_1 v_2^{1/3}/[\ln (1 - v_2) + v_2 + \mu v_2^2] \quad (20)$$

where v_2 now represents the volume fraction at swelling equilibrium. Hence, given the value of the parameter μ for a given solvent–polymer pair it is possible to calculate the average molecular weight per chain, or the effective concentration of cross-linkages, from the equilibrium swelling volume. For sufficiently large degrees of swelling (small v_2) the quantity in brackets in equation 20 may be approximated by the first term in its series expansion, $v_2^2(1 - 2\mu)/2$, giving

$$M_c \cong 2\rho V_1/v_2^{5/3}(1 - 2\mu) \quad (21)$$

or

$$v_2 \cong [2\rho V_1/M_c(1 - 2\mu)]^{3/5} \quad (22)$$

Hence the swelling volume ratio, $1/v_2$, is proportional to the three-fifths power of the molecular weight per chain.

Substituting equation 20 in equation 9' to obtain the relationship between tension in stretched rubber and equilibrium swelling

$$\tau = -[RT\varphi(\alpha)/V_1 v_2^{1/3}][\ln (1 - v_2) + v_2 + \mu v_2^2] \quad (23)$$

or

$$\tau \cong RT\varphi(\alpha)(1 - 2\mu)v_2^{5/3}/2V_1 \quad (24)$$

According to this relationship the tension at a given elongation, or "modulus," should be approximately inversely proportional to the five-thirds power of the swelling volume ratio in a given solvent.

2. Comparison with experiment

Experimental results on Butyl rubber pure gum vulcanizates are in good agreement with this relationship. This is shown in figure 8, where the log of the "modulus" at 300 per cent elongation ($\alpha = 4$) is plotted against the log of the swelling volume ratio in cyclohexane at 25°C. The points represent rubbers differing both in initial molecular weight and in degree of cross-linking. The straight line in figure 8, drawn with the theoretical slope of $-5/3$, is matched by the points within experimental error. Taking $V_1 = 110$ cc., the position of this line yields for μ the reasonable value of 0.3 (18) for solutions of Butyl polymers in cyclohexane.

The success of the theory in relating swelling to elastic modulus shows that the

same network cross-linkage and entanglements are operative both in swelling and in stretching. If the excess in the modulus over that which would be calculated from the number of primary valence cross-linkages has been correctly attributed to entanglements, these same entanglements produce an equivalent reaction to expansion of the network by a solvent. Similarly, it follows from the above correlation that the effect on equilibrium swelling of molecular weight prior to vulcanization parallels its effect on elastic retractive force as previously discussed. In the equations given above, therefore, the
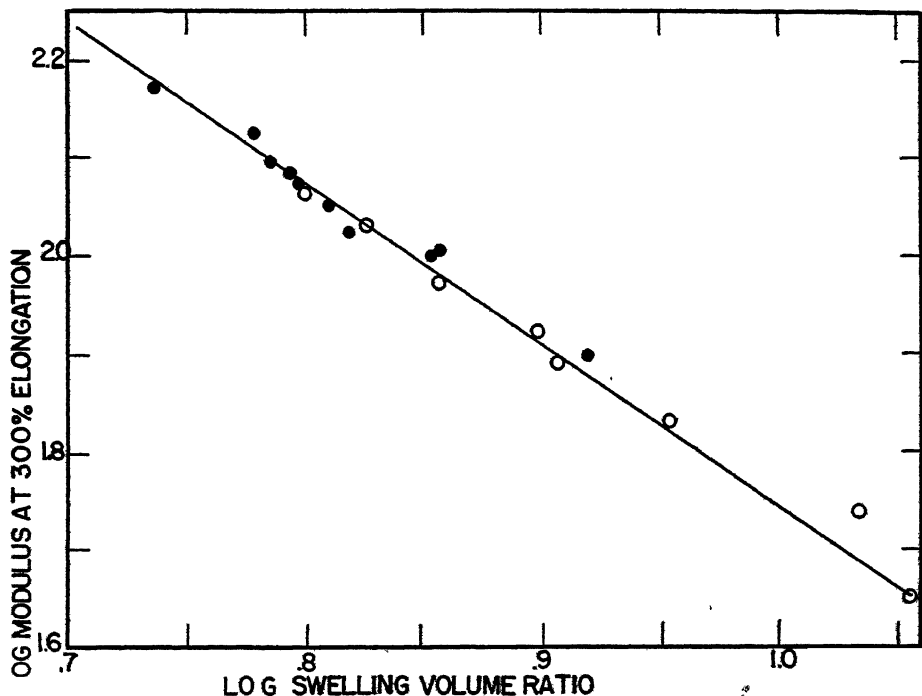
Fig. 8. Relationship between "modulus" and swelling volume ratio $(1/v_2)$ for various pure gum Butyl vulcanizates. O = low unsaturation series; ● = high unsaturation series.

effective number of chains should be employed. For example, in place of equations 17 we have

$$\Delta F_e = (3kTg\nu_0/2)(1 - 2M_c/M)\{[(Z_0\nu_0 + n)/Z_0\nu_0]^{2/3} - 1\} \qquad (17')$$

and in subsequent equations M_c should be replaced by $M_c/g(1 - 2M_c/M)$. The equation for equilibrium swelling becomes

$$v_2 = [2\rho V_1 g(1 - 2M_c/M)/M_c(1 - 2\mu)]^{3/5} \qquad (22')$$

If secondary valence cross-linkages between chains were to contribute to the modulus in deformation, these bonds would be expected to dissociate in the presence of a solvent and the above correlation between swelling equilibrium and

modulus would be destroyed.   These results constitute strong evidence against the existence of van der Waals cross-linkages in vulcanized rubber.

VII. SUMMARY

Current concepts of the network structure of vulcanized rubber have been reviewed and various recent theoretical treatments of the rubber elasticity problem have been compared.   These are found to be in essential agreement; they represent merely different methods of analysis of equivalent physical concepts.

The theoretically derived equation for the elastic retractive force in stretched rubber consists of two factors, one of which is a function of the relative length (α) alone, and the other of which is proportional to the "effective" number of cross-linkages in the network and is independent of the deformation.   (The latter factor also contains the absolute temperature.)   Experimental results are in agreement with this separability of the elongation and structure factors; i.e., the *shape* of the stress–strain curve (short of the region of crystallization) is preserved as the effective number of cross-linkages in the vulcanizate is varied.

The observed magnitude of the retractive force at a given elongation is appreciably greater than that calculated from the independently estimated number of chemical cross-linkages in vulcanizates of Butyl rubber.   This discrepancy is believed to be due to entanglements of the chains which increase the effective number of cross-linkages.   The observed effect of the molecular weight of the rubber before vulcanization on elastic properties of the vulcanizate has been taken into account by an extension of previous theories.   The "flaws" introduced into the network by the ends of the molecules of rubber diminish the effective number of cross-linkages.   The theoretically derived factor which expresses this dependence on initial molecular weight is in good agreement with experiment.

The swelling capacity of vulcanized rubber in solvents, like the elastic modulus, is related to the number of effective cross-linkages.   Hence, modulus and swelling capacity can be related to one another.   The equation expressing this relationship is amply confirmed by experimental results.   From this it is concluded that the same cross-linkages are effective in the presence of solvents which swell the rubber as are operative in the reaction of the rubber to elastic deformation.

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HETEROCYCLIC NITROGEN COMPOUNDS[1]

EDWARD CURTIS FRANKLIN and F. W. BERGSTROM

PART II A. HEXACYCLIC COMPOUNDS: PYRIDINE, QUINOLINE, AND ISOQUINOLINE

F. W. BERGSTROM

Department of Chemistry, Stanford University, California

CONTENTS

In this article "ammono aquo" is used rather than "aquo ammono", in order to conform to the usage adopted by *Chemical Abstracts*.

I. INTRODUCTION

It is the purpose of the present review to summarize a portion of the chemistry of six-membered heterocyclic compounds containing nitrogen and to interpret the reactions insofar as possible from the standpoint of the nitrogen or ammonia system of compounds (323). The extent of the field to be covered imposes necessary limitations upon the number of heterocyclic types to be discussed, in order to prevent an unwieldy review. Accordingly there will be considered only compounds containing one heterocyclic ring with either one or two hetero nitrogen atoms; omissions will be dealt with in a future paper.

Careful reading of the chemical literature soon makes it apparent that the explanation of reactions of pyridine, quinoline, and isoquinoline in terms of an ammonia system is often merely a restatement—in different language—of theories that have long before been expressed, or have otherwise acquired common acceptance as the result of the work of a number of investigators. Thus, the

similarity of the reactions of α- and γ-methylpyridines or α- and γ-methylquinolines to those of the methyl ketones was recognized as long ago as 1901 by Koenigs (493) and has since been commented upon by numerous observers, including Chichibabin (115) and Mills and Smith (621a). Furthermore, pyridine and quinoline have from time to time been called cyclic Schiff bases, with the implication that, like the latter, they may have certain chemical properties in common with the aldehydes and ketones.

A proper understanding of the viewpoint of this article makes desirable a brief explanation of the nitrogen or ammonia system of compounds. Within the next few pages, therefore, will be discussed the majority of the chemical types that will be encountered further on.

A. BASES OF THE AMMONIA SYSTEM

Bases of the water system, such as potassium hydroxide, KOH, and sodium hydroxide, NaOH, are derived from the parent solvent, water, by replacement of one hydrogen atom by an univalent metal. Similarly, by replacement of a hydrogen atom of ammonia, one obtains the ammono bases, potassium amide, KNH_2, and sodium amide, $NaNH_2$. Ammono bases are as a rule much more reactive than aquo bases, and for this reason are of considerable value in organic synthesis. The following comparison will illustrate this point.

Aryl halides are rapidly attacked by the alkali amides in liquid ammonia solution at $-33°C$. or at room temperatures to give metallic salts of the corresponding aryl amines, in accordance with the equation (65a, 820a):

$$C_6H_5Cl + 2KNH_2 \rightarrow C_6H_5NHK + KCl + NH_3 \tag{1}$$

Diphenylamine, triphenylamine, and p-aminobiphenyl are formed simultaneously by reactions that are dependent upon the catalytic effect of the potassium amide.

The related reaction of the water system, the conversion of chlorobenzene to phenol or sodium phenoxide by sodium carbonate or sodium hydroxide, requires a temperature of about $320°C$. and a pressure of 3000 pounds per square inch (380).

B. ACIDS OF THE AMMONIA SYSTEM

Substances having acidic properties in water will behave as acids in liquid ammonia if they have sufficient solubility. In water and in liquid ammonia the hydrogen ion is solvated to the oxonium and ammonium ions, respectively. The oxonium or "hydrogen" ion in water has an abnormally high conductance, several times that of other ions, while the ammonium ion in liquid ammonia is normal in behavior. It is therefore not surprising to find that all ammonium salts in liquid ammonia are very weak acids.

The true acids of the ammonia system contain nitrogen and are related to ammonia as are the familiar oxygen acids to water. The "hydrogen ions" into which these acids dissociate are, of course, solvated to ammonium ions, though generally the ammonium salts of these ammono acids cannot be isolated under ordinary conditions. Although the acids listed below all show definite acidic properties in liquid ammonia, several behave as bases when dissolved in water (guanidine, the amidines):

Benzoic acids

C_6H_5COOH $C_6H_5C(=NH)NH_2$ $C_6H_5CONH_2$

Aquobenzoic acid   Ammonobenzoic acid   Ammonoaquobenzoic acid
                          or benzamidine   or benzamide

In ammonobenzoic acid, the divalent oxygen and the monovalent hydroxyl group have been both replaced by the corresponding valence-equivalent residues of ammonia; in benzamide, this replacement is only partial.

It will be noted that ammonobenzoic acid is formally tribasic, although it is possible only to prepare a monopotassium salt, $C_6H_5C(=NH)NHK$. The trivalence of nitrogen, as contrasted with the divalence of oxygen, increases the complexity of the compounds of the ammonia system.

Carbonic acids

$CO(OH)_2$ $NH=C(NH_2)_2$ $N\equiv C-NH_2$ $NH=C\begin{smallmatrix}NH_2\\NHCN\end{smallmatrix}$

Aquocarbonic   Guanidine   Cyanamide   Dicyanodiamide
acid (unstable)

Ammonocarbonic acids

$CO(NH_2)_2$ HNCO $NH_2CONHCONH_2$

Urea   Cyanic acid   Biuret

Ammonoaquocarbonic acids

While there is but one aquocarbonic acid (this can exist only in solution), there are many ammonocarbonic acids, of which only three are listed (322).

Dicyanodiamide and biuret represent a class of compounds often encountered in the water system,—the pyro acids, of the type of pyrosulfuric acid, $H_2S_2O_7$, or pyrophosphoric acid, $H_4P_2O_7$. Just as pyrosulfuric acid is formed by loss of water between two molecules of sulfuric acid, so dicyanodiamide may be regarded as formed by the loss of ammonia between two ammonocarbonic acids, cyanamide and guanidine. The parallel relationships are shown below:

$$2HOSO_2OH = H_2O + HOSO_2-O-SO_2OH$$

$$CNNH_2 + NH_2C(=NH)NH_2 = CNNHC(=NH)NH_2 + NH_3$$
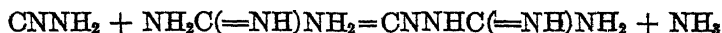
A few heterocyclic nitrogen compounds that may be regarded as acids of the ammonia system are listed below:
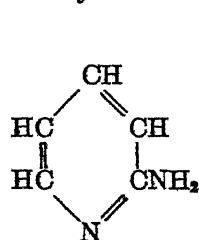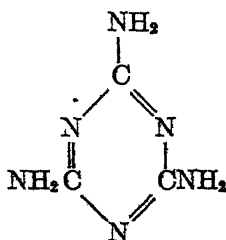
2-Aminopyridine   Melamine   2-Aminoquinoline
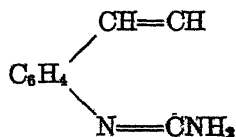
2-Aminopyridine and 2-aminoquinoline contain the grouping —C(NH₂)=N—, characteristic of ammonobenzoic acid and related compounds. One hydrogen attached to nitrogen has, however, been replaced by a group (that is, by one side of the ring), and so both of the substances above are cyclic ammono acid esters.

Melamine is a cyclic ammonopyrocarbonic acid, formed theoretically by the loss of three molecules of ammonia from three molecules of the ammonocarbonic acid, guanidine. It is actually best prepared from cyanamide or dicyanodiamide.

C. ALCOHOLS OF THE AMMONIA SYSTEM

The alkylamines are alcohols of the ammonia system.

C_2H_5OH $C_2H_5NH_2$ $(C_2H_5)_2NH$

Primary aquo alcohol   Primary ammono alcohols

$(CH_3)_2CHOH$ $(CH_3)_2CHNH_2$ $(CH_3)_2CHNHCH(CH_3)_2$

Secondary aquo alcohol   Secondary ammono alcohols

$(CH_3)_3COH$ $(CH_3)_3CNH_2$ $(CH_3)_3CNHC(CH_3)_3$

Tertiary aquo   Tertiary ammono alcohols
alcohol

$CH_3CH_2NHCH(CH_3)_2$

Mixed primary–secondary
ammono alcohol

It is evident that in the ammonia system, as in the water system, the class to which an alcohol belongs is dependent upon the carbon atom to which the amino or imino group is attached. Mixed ammono alcohols of the type of ethylisopropylamine (above) may exist.

Diethylamine is really an alcohol rather than an ether, because of the hydrogen attached to nitrogen, which makes reactions similar to that of equation 2 possible (824).

$$(C_2H_5)_2NH + LiC_6H_5 = C_6H_6 + (C_2H_5)_2NLi \qquad (2)$$
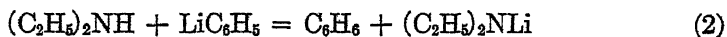
The formation of lithium diethylamide is to be compared to the action of an alkali-metal aryl upon an aquo alcohol to give a hydrocarbon and a metal alkoxide.

D. ETHERS OF THE AMMONIA SYSTEM

When both hydrogen atoms of water are replaced by groups, an ether is formed; similarly, when all three hydrogens of ammonia are replaced, an ammono ether is obtained.

$(C_2H_5)_2O$ $(CH_3)_3N$
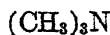
Aquo ether   Ammono ether   Ammono ether
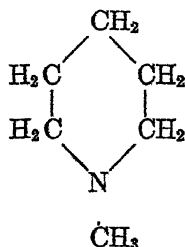
Strictly speaking, a secondary amine might be considered as a mixed ammono ether alcohol.

E. ALDEHYDES, MEROACETALS, ACETALS

C_6H_5 CHO

Aquo aldehyde

C_6H_5 CH=NH

Ammono aldehyde alcohol
(benzylidenimine)

C_6H_5 CH=NC_6H_5

Ammono aldehyde ether
(benzalaniline)

Since nitrogen is trivalent, while oxygen is divalent, all aldehydes of the ammonia system are mixed compounds of the kind shown above. It should be noted that the hydrogen attached to nitrogen in benzylidenimine is arbitrarily called "alcoholic"; it may be replaced by an alkali metal, but this replacement has considerable influence on the aldehydic reactivity (781).

Strain has thus found that benzylidenimine undergoes the Cannizzaro reaction when heated with a solution of potassium amide in liquid ammonia at 210°C. for 1 day. Benzalaniline will, however, react similarly at room temperatures (783).

The negative charge on the anion of the alkali-metal salt, $(C_6H_5CH=N^-)K^+$, doubtless is responsible for slowing down a reaction that involves the highly active amide ion, NH_2^-, of potassium amide.

Many cyclic nitrogen compounds, including pyridine, quinoline, and isoquinoline, are to be regarded as cyclic ammono aldehyde ethers.
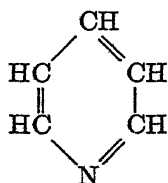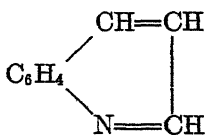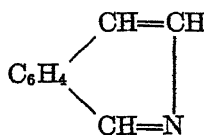
Pyridine   Quinoline   Isoquinoline

Some aldehyde derivatives are listed below:

CCl_3 CH(OH)$_2$
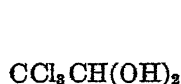
Aquo aldehyde
hydrate
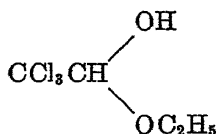
Aquo aldehyde
alcoholate
(hemiacetal)
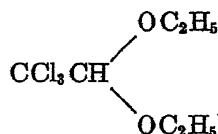
Aquo acetal
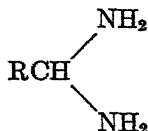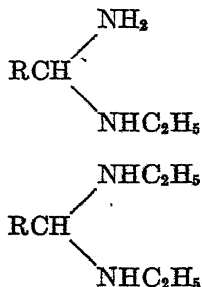
Ammono aldehyde   Ammono meroacetals

$$\underset{\text{Ammono acetal}}{RCH\Big\langle{\overset{\displaystyle N(C_2H_5)_2}{N(C_2H_5)_2}}}$$
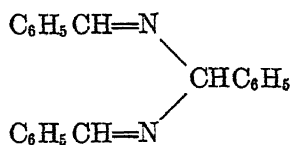
$$\underset{\substack{\text{Ammono aldehyde acetal} \\ \text{(hydrobenzamide)}}}{\overset{\displaystyle C_6H_5CH{=}N}{\underset{\displaystyle C_6H_5CH{=}N}{\Big\rangle}}CHC_6H_5}$$

$$\underset{\substack{\text{Ammono aquo meroacetals}}}{RCH\Big\langle{\overset{\displaystyle OH}{NHC_2H_5}}\qquad RCH\Big\langle{\overset{\displaystyle OH}{N(C_2H_5)_2}}}\qquad \underset{\text{Ammono aquo acetal}}{RCH\Big\langle{\overset{\displaystyle OC_2H_5}{N(C_2H_5)_2}}}$$
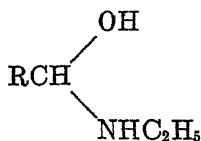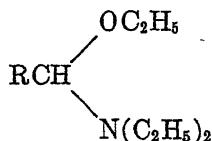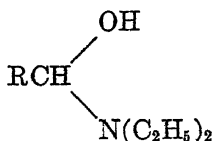
While chloral alcoholate (above) is a true half- or hemi-acetal, the related compounds of the ammonia system, or the mixed ammono aquo compounds, are quarter-, third-, three-quarter-, or half-acetals. It is proposed, for the purposes of a simplified nomenclature, to call all substances between the aldehyde solvate (such as chloral hydrate) and the acetal, meroacetals, from the Greek *meros*, meaning a part or a fraction.

Hydrobenzamide contains two —CH=N— groups and is therefore an ammono aldehyde; since one of the three C_6H_5CH groups is attached to two nitrogens, hydrobenzamide is at the same time an acetal.

Heterocyclic compounds which are to be considered aldehyde derivatives are known in abundance; a few are listed.
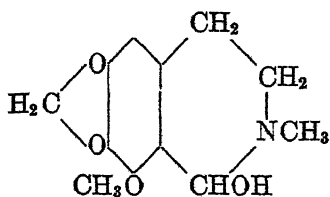
Cotarnine
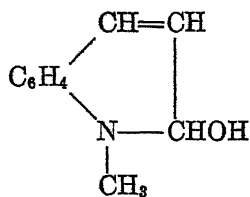
1-Methyl-2-hydroxy-1,2-dihydroquinoline (a pseudo base)

Cyclic ammono aquo meroacetals
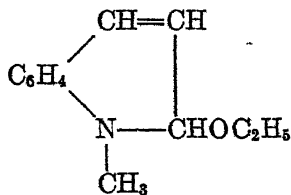
1-Methyl-2-ethoxy-1,2-dihydroquinoline (a cyclic ammono aquo acetal)

F. KETONES OF THE AMMONIA SYSTEM

$(CH_3)_2CO$ $(C_6H_5)_2C\!\!=\!\!NH$ $(C_6H_5)_2C\!\!=\!\!NC_6H_5$

Aquo ketone   Ammono ketone alcohol   Ammono ketone ether
(acetone)   (benzophenonimine)   (benzophenone anil)

Some cyclic ammono ketone ethers are 2-picoline, quinaldine, 2-phenylquinoline, and 2,3-dimethylquinoxaline, whose formulas are given below:
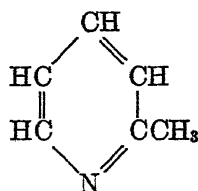
2-Picoline   Quinaldine
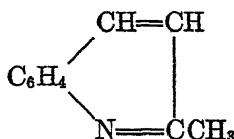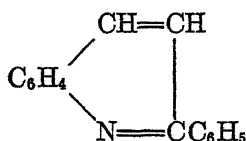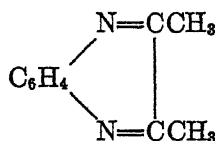
2-Phenylquinoline   2,3-Dimethylquinoxaline

Of these four compounds, all but 2-phenylquinoline are analogues of a methyl ketone of the water system.

G. ESTERS OF THE AMMONIA SYSTEM

Ethyl benzoate   Triphenylbenzamidine   Benzimino ethyl ether
(an aquo ester)   (an ammono ester)   (an ammono aquo ester)

$CO(OC_2H_5)_2$ $CO(NR_2)_2$ $N\!\!\equiv\!\!CN(C_2H_5)_2$
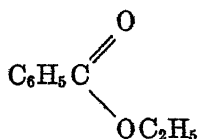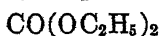
Diethyl carbonate   A tetrasubstituted urea   Diethylcyanamide
(an aquo ester)   (an ammono aquo ester)   (an ammono ester)
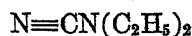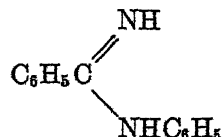
Monoethyl oxalate   sym-Dimethylurea   N-Phenylbenzamidine
(an aquo acid ester)   (an ammono aquo acid ester)   (an ammono acid ester)

The simplest acid ester of the water system is monoethyl oxalate; similar compounds of the ammonia or mixed water–ammonia systems will also be acid esters, as will substances of the type of sym-dimethylurea and N-phenylbenzamidine,

which still have hydrogens attached to nitrogen. Some analogues of the above among the cyclic compounds are the following:
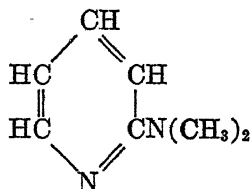
2-Dimethylaminopyridine
(a cyclic ammono ester)
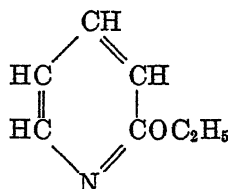
2-Ethoxypyridine
(a cyclic ammono
aquo ester)
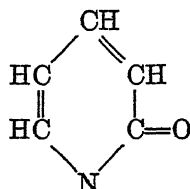
1-Methyl-2-pyridone
(a cyclic ammono
aquo ester)
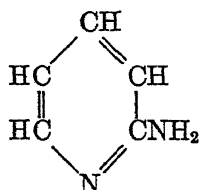
2-Aminopyridine   2-Methylaminopyridine
(cyclic ammono acid esters)

It is desirable to emphasize again the fact that the ammono acids analogous to the carboxylic acids, RCOOH, have the formula $RC(=NH)NH_2$ and are tribasic. 2-Aminopyridine has one of these hydrogens replaced by a group, and is therefore an acid ester.

H. ACID ANHYDRIDES AND ACID ANAMMONIDES

An acid anhydride, such as acetic anhydride, is derived from two molecules of a carboxylic acid by loss of one molecule of water; related acids of the ammonia system, the amidines, can lose ammonia intramolecularly to give an acid anammonide, in this case, a nitrile.

$$2CH_3COOH - H_2O = CH_3CO-O-COCH_3$$

$$CH_3C(=NH)NH_2 - NH_3 = CH_3CN$$
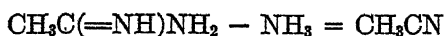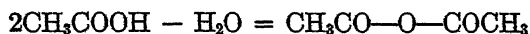
Triacetamide, $(CH_3CO)_3N$, is an acid anhydride anammonide, while cyaphenine
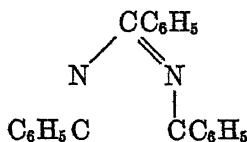
is a cyclic anammonide of ammonobenzoic acid (or benzamidine).

I. TRANSMISSION OF EFFECTS ALONG A CONJUGATED CHAIN; EXPANDED SYSTEMS; THE PRINCIPLE OF VINYLOGY

During the period from 1917 to 1924, Angeli (12) wrote a series of articles in which he showed that the behavior of an ortho- or para-disubstituted benzene could be approximated by joining the two substituent groups together. The o- and p-nitrochlorobenzenes, accordingly, should behave like nitryl chloride, NO_2Cl, the acid chloride of nitric acid (doubt has been expressed as to whether or not this has ever been isolated in the pure condition, so its properties are not known with certainty). Nevertheless, although their reactivity is above that of m-nitrochlorobenzene, it is considerably below that of a typical acid chloride. One might say that the chlorine and the nitro group mutually affect each other across the conjugated system of the benzene ring, but with considerable damping. The o- and p-nitrotoluenes should have reactive methyl groups because of resemblance in this sense to nitromethane, CH_3NO_2; to some extent the predicted reactivity has been observed.

Fuson (359) has generalized this phenomenon in the following words:

"When in a compound of the type, A—E_1=E_2, or A—E_1≡E_2, a structural unit of the type,
$$-(\overset{|}{C}=\overset{|}{C})_n-$$ is interposed between A and E_1, the function of E_2 remains qualitatively unchanged but that of E_1 may be usurped by the carbon atom attached to A. The resulting compound will have the form, A—$(\overset{|}{C}=\overset{|}{C})_n$—$E_1$=$E_2$ or A—$(\overset{|}{C}=\overset{|}{C})_n$—$E_1$≡$E_2$, and in any given series of this type the members will differ from each other by one or more vinylene residues (disposed in a linear arrangement). It is proposed to term such a group of compounds a vinylogous series. The members of a vinylogous series will be vinylogues of each other."

This rule will therefore not only cover such cases as those of the o- and p-nitrochlorobenzenes, but also straight-chain compounds of the type of ethyl crotonate (I), ethyl sorbate (II), and crotononitrile (III), all of which contain reactive methyl groups.

$$CH_3CH=CHCOOC_2H_5 \qquad CH_3CH=CH-CH=CH-COOC_2H_5$$
$$I \qquad\qquad\qquad\qquad II$$
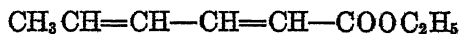
$$CH_3CH=CHCN$$
$$III$$

The first two are "vinylogues" of ethyl acetate, the latter a vinylogue of acetonitrile (360). Their behavior is approximated by uniting the two groups attached to the ends of the conjugated system.

The English chemists have for years recognized the fact that effects could be transmitted along a conjugated chain; the following explanation of this transmission is worthy of repetition (442a, 472a, 713a, 713b):

In the compound

$$Cl-\underset{1}{CH}=\underset{2}{CH}-\underset{3}{CH}=\underset{4}{CH}-\underset{5}{CH}=\underset{6}{CH}-$$
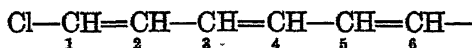
the chlorine has three pairs of unshared electrons. Under certain circumstances, two of the unshared electrons of the chlorine may become shared with carbon atom 1, giving at first:

$$\overset{+}{Cl}=CH=CH-CH=CH-CH=CH-$$
$$_1_2_3_4_5_6$$
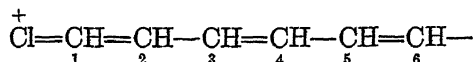
The chlorine has lost a half interest in two electrons, and so bears a positive charge, but carbon atom 1 now has a decet of electrons around it. Since carbon in combination normally has an octet of electrons in its outer shell, further changes must occur. Two things may happen: (a) Two electrons, shared originally by C-1 and C-2 may be shifted so that they are shared between C-2 and C-3, that is to say, the double bond shifts and the shift will continue along the chain to give

$$\overset{+}{Cl}=CH-CH=CH-CH=CH-CH=$$
$$_1_2_3_4_5_6$$
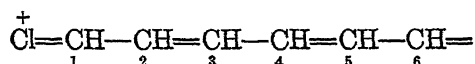
(b) An electron pair of a double bond may become unshared on one of the even-numbered carbon atoms, as in the example:

$$\overset{+}{Cl}=CH\overset{\frown}{=}\overset{-}{CH}-CH=CH-CH=CH-$$
$$_1_2_3_4_5_6$$
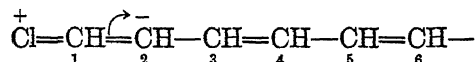
The curved arrow is intended to show this unsharing, which gives an integral (−) charge to C-2. The electron pair concerned has at no time left the octet of C-2, yet it is not now a part of the octet of C-1.

Groups such as methyl repel electrons slightly (+I effect; see references 442, 442a, 713a, 713b) and initiate a change that is similarly transmitted along the conjugated chain.

The effect of a nitro group is, conversely, to attract electrons and either cause a shift of the double bonds or the appearance of positive charges (at intervals, of course) upon the even-numbered carbons of the chain. These carbons will then have only a sextet of electrons. The changes may be represented in the abbreviated fashion of the English chemists in the manner shown below:

$$\begin{array}{c} O \\ \diagdown \\ N\!\!\overset{\frown}{-}CH\!\!\overset{\frown}{=}CH\!\!\overset{\frown}{=}CH\!\!\overset{\frown}{=}CH\!\!\overset{\frown}{-}CH\!\!\overset{\frown}{=}CH- \\ /\!\!/ \\ -O \end{array}$$

$$\begin{array}{c} O \\ \diagdown \\ N\!\!\overset{\frown}{-}CH\!\!\overset{\frown}{=}\overset{+}{CH}-CH=\overset{\cdot}{CH}-CH=(\\ /\!\!/ \\ -O \end{array}$$
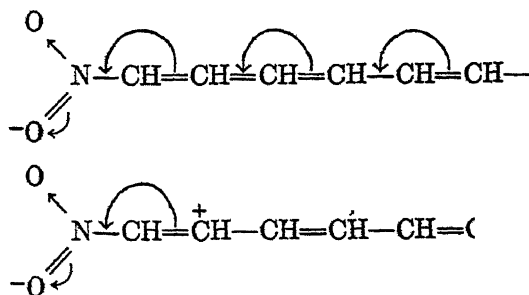
In the lower formula, carbon No. 2 has a positive charge.

In view of the foregoing, it often happens that heterocyclic nitrogen compounds show reactivity at points other than those predicted from their relation-

ship to the nitrogen system. 4-Methylpyridine and lepidine have many of the ketonic properties of 2-methylpyridine and of quinaldine. 2-Phenylquinoline is a cyclic ammono ketone ether, yet the 4-position often behaves like the 2-position in quinoline itself, as is shown by the reactions with potassium amide and potassium nitrate in liquid ammonia (see Section IV, K).

J. RESONANCE AND RING STABILITY

Nearly all of the ring compounds discussed in this review have the bond system of benzene or its homologues, and consequently have considerable resonance energy. The values in the table below have been taken from Pauling (673) and from Miss Wrinch (in parentheses (821); these are estimated minimum values).

Resonance energy

kilocalories per mole

Benzene	.39 (56)
Pyridine	43 (54)
Naphthalene	.75 (103)
Quinoline	.69 (91)

The resonance energy of a nitrogen heterocycle is not far from that of its closest carbocyclic analogue. It follows that pyridine, quinoline, isoquinoline, and related compounds will have a reactivity much less than that of open-chain analogues of either the water or the ammonia system, even though the syntheses of these heterocyclic compounds are in full agreement with their assumed relationship to the ammonia system.

It is unfortunate that many of the original journals, including the Russian, have been unavailable during the writing of this review. It has been necessary to depend upon abstracts not only for these but also for patents.

II. PYRIDINE

A. RELATIONSHIP TO THE NITROGEN OR AMMONIA SYSTEM

The true relationship of pyridine to the ammonia system is shown by its formation from glutacondialdehyde in accordance with the equation:

$$CHOCH_2CH=CHCHO \rightleftarrows CHOH=CHCH=CHCHO \quad \begin{matrix} N\dot{H}_2 \\ -2H_2O \end{matrix}$$
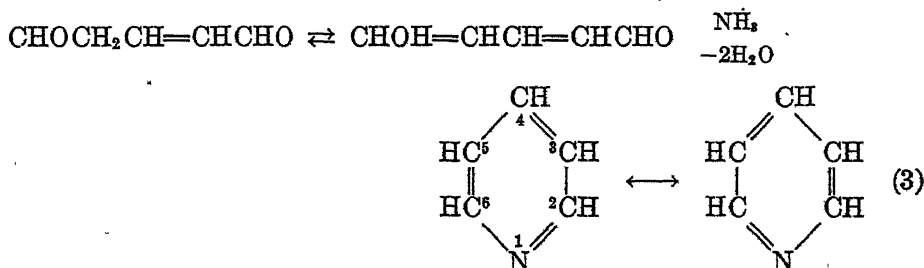
(see also Section II, B, (1) and (2)). Pyridine is therefore to be regarded as an anammonide of the ammono aldehyde enol, $NH_2CH=CHCH=CHCH=NH$. It is simpler and sufficiently accurate, however, to regard pyridine as a cyclic

ammono aldehyde ether, since it contains the grouping —CH=NR, characteristic of these compounds. The equivalence of the 2- and 6-positions may then be explained on the basis of a resonance between the two forms shown above.

2-Alkylated (I) or 2-arylated (II) pyridines are cyclic ammono ketone ethers, but because of the transmission of effects along a conjugated chain, the 4- and 6-positions will have some of the function of the 2-position of unsubstituted pyridine.

<div align="center">
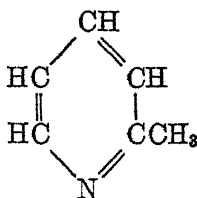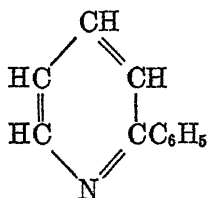
```
       CH                          CH
      /  ‖                        /  ‖
   HC    CH                    HC    CH
    ‖     |                     ‖     |
   HC    CCH₃                  HC    CC₆H₅
      \  //                       \  //
        N                           N

        I                          II
   2-Picoline                 2-Phenylpyridine
```

</div>

This is readily seen if one or two —C=C— groups are removed from the formulas of 2-picoline (I) or 2-phenylpyridine (II), respectively, leaving $CH_3CH=N—$ and $C_6H_5CH=N—$, which are ammono aldehyde ethers.

Along the same lines, an alkyl or aryl group in position 4 will have the function of the same group in position 2, while both groups of a 2,6-disubstituted pyridine will be equivalent, if they are the same. 4-Methylpyridine (4-picoline), as anticipated, has pronounced ketonic properties, though there has been some loss in the effect of the —C=N— linkage on the methyl by damping; both methyl groups of 2,6-dimethylpyridine are equally reactive.

2-Chloropyridine (III) is a cyclic ammono acid chloride ester, while 4-chloropyridine (IV) is its vinylogue.

<div align="center">
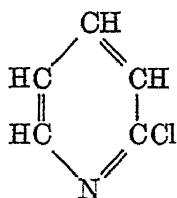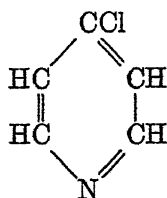
```
       CH                          CCl
      /  ‖                        /  ‖
   HC    CH                    HC    CH
    ‖     |                     ‖     |
   HC    CCl                   HC    CH
      \  //                       \  //
        N                           N

       III                         IV
  2-Chloropyridine           4-Chloropyridine
```

</div>

Because of the trivalence of nitrogen it is not possible to have a strict nitrogen analogue of an aquo acid chloride, RCOCl, since one hydrogen will remain as in RC(=NH)Cl (an ammono acid chloride acid) or else the nitrogen will be attached to a group, RC(=NR)Cl, to give an ammono acid chloride ester.

Some additional pyridine derivatives are listed below, with indicated relationship to the ammonia system.
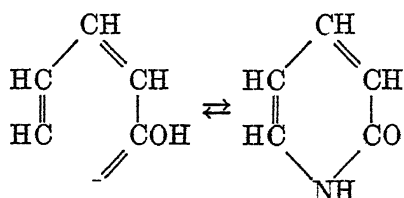
V
2-Hydroxypyridine or 2-pyridone
(cyclic ammono aquo acid esters)
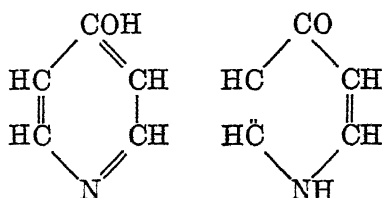
VI
4-Hydroxypyridine or 4-pyridone
(vinylogues of V)
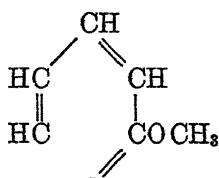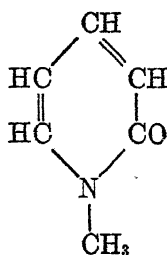
2-Methoxypyridine   1-Methyl-2-pyridone
(cyclic ammono aquo esters)

B. METHODS OF SYNTHESIS

Here and later no attempt will be made to cover completely the syntheses of the heterocyclic compounds. Generally, the methods given will be of somewhat greater interest from the point of view of the ammonia system.

(1) Glutacondialdehyde and its derivatives are readily converted to pyridines by the action of ammonia under rather mild conditions. This reaction has previously been discussed, and is represented by equation 3.

(2) γ-Pyrone and substituted pyrones are ammonolyzed when heated with aqueous or alcoholic ammonia with the formation of γ-pyridones in accordance with the equation:

$$+ NH_3 = H_2O + \qquad\qquad (4)$$
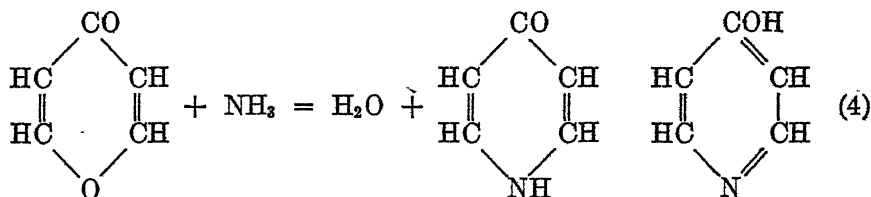
Pyridone is thus made by heating γ-pyrone with aqueous ammonia at 120–140°C. for 6 hr. (382, 473a, 683), while 2,3-dimethyl-γ-pyridone is similarly prepared from 2,6-dimethyl-γ-pyrone (766) (for the preparation of α-pyridone, see reference 677). In these reactions, the ring is presumably opened by the action of ammonia, and then closed again with the elimination of water. γ-Pyrone is to be regarded as the cyclic anhydride of the dienol form of 1,5-pentanedial-3-one.

$$O=C \begin{array}{c} CH_2CHO \\ \\ CH_2CHO \end{array} \rightleftarrows CO \begin{array}{c} CH=CHOH \\ \\ CH=CHOH \end{array} \xrightarrow{-H_2O} O=C \begin{array}{c} CH=CH \\ \\ CH=CH \end{array} O$$
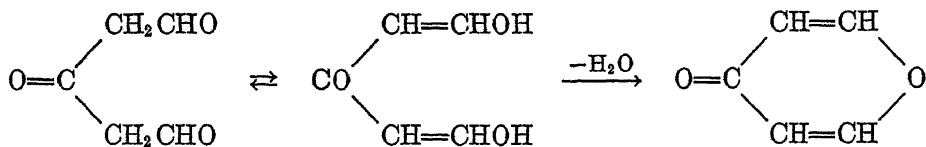
The relationship to synthesis (*1*) is readily seen.

(*3*) Pyrylium salts, when warmed with ammonia, give pyridines in the manner of the following equation (27a, 247, 248, 248a; + $C_6H_5NHNH_2$, 745):

+ 2NH₃

ClO_4^-
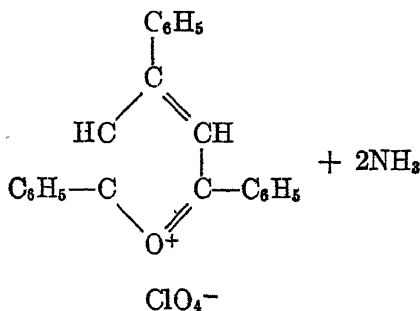
2,4,6-Triphenylpyrylium perchlorate

$$NH_4ClO_4 + H_2O + $$

(5)

2,4,6-Triphenylpyridine
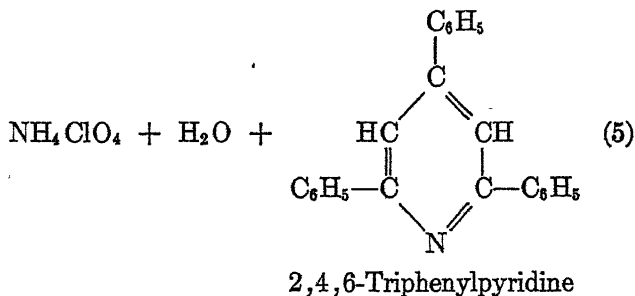
The relationship of pyrylium salts to the pyridines is accordingly a close one; a more extended discussion will be found in Section III.

(*4*) The classical pyridine synthesis of Hantzsch (404b; *cf.* 405a) is illustrated by the preparation of 2,4,6-trimethylpyridine (*sym*-collidine), which proceeds in accordance with the equations below:

−3H₂O

$$
\begin{array}{c}
CH_3 \\
| \\
CH \\
C_2H_5OOC-C \qquad C-COOC_2H_5 \\
\;\; \| \qquad\qquad \| \\
CH_3-C \qquad C-CH_3 \\
NH
\end{array}
\xrightarrow{\;HONO\;}
$$

I

$$
\begin{array}{c}
CH_3 \\
| \\
C \\
C_2H_5OOC-C \qquad C-COOC_2H_5 \\
\;\; \| \qquad\qquad \\
CH_3-C \qquad C-CH_3 \\
\end{array}
\xrightarrow[\text{heat}]{\;NaOH\;}
$$

II

$$
\begin{array}{c}
CH_3 \\
| \\
C \\
NaOOC-C \qquad C-COONa \\
\;\; \| \qquad\qquad \| \\
CH_3-C \qquad C-CH_3 \\
N
\end{array}
\xrightarrow{\;\text{acidify}\;}
$$

$$
\text{free acid} \xrightarrow[-2CO_2]{\;\text{heat}\;}
\begin{array}{c}
CH_3 \\
| \\
C \\
HC \qquad CH \\
\;\; \| \qquad\qquad \| \\
CH_3-C \qquad C-CH_3 \\
N
\end{array}
\qquad (6)
$$

III
Collidine
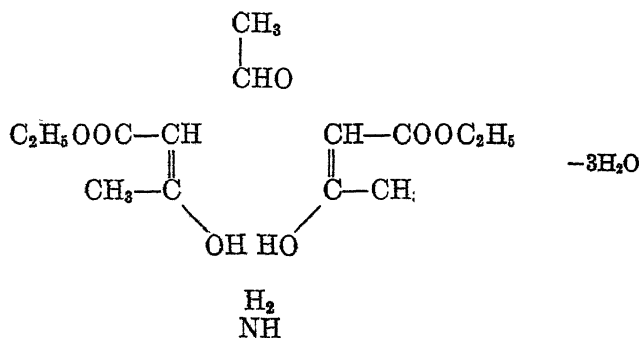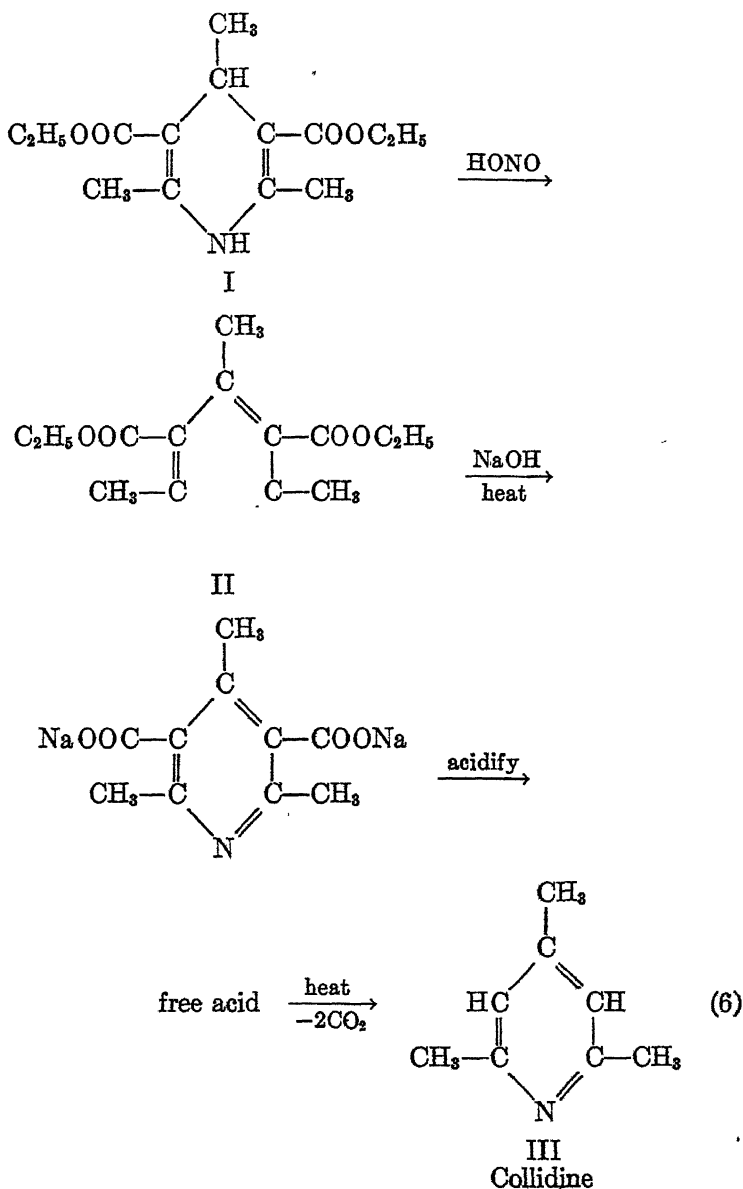
Two moles of ethyl acetoacetate (written in the enol form) react with 1 mole each of acetaldehyde and ammonia (=aldehyde-ammonia) to form dihydro-collidinedicarboxylic ester (I), which is generally considered a derivative of 1,4-dihydropyridine (cf. 763c; for the relationship of 1,4-dihydropyridines to the nitrogen system, see Section II, C, (g)). Oxidation with nitrous acid ("nitrous fumes") gives collidinedicarboxylic ester (II), and this may be converted to collidine (III) by saponification and subsequent decarboxylation of the resulting acid.

Oxidation of the dihydro ester (I) to the pyridinedicarboxylic acid ester (II) often cannot be accomplished by nitrous acid; the use of nitric acid, chromic acid, hydroxylamine hydrochloride, and even of sulfur (at 150°C.) (but not of potassium permanganate or iodine) has been recommended (*cf.* 43d, 426a, 763a).

The Hantzsch synthesis is capable of considerable variation, both in the nature of the aldehyde and the β-ketonic ester or β-diketone used, and in the details of carrying out the reactions. The mechanism is expressed by one or the other of the two sets of equations below:

$$CH_3COCH_2COOC_2H_5 + RCHO \rightarrow CH_3COC(=CHR)COOC_2H_5 + H_2O$$

$$IV$$

$$CH_3COCH_2COOC_2H_5 + NH_3 \rightarrow$$
$$V$$

$$CH_3C(=NH)CH_2COOC_2H_5 \rightleftarrows CH_3C(NH_2)=CHCOOC_2H_5$$
$$IX \qquad\qquad X$$

$$
\begin{array}{c}
\text{R}\\
|\\
\text{CH}\\
\diagup\;\diagdown\\
\text{C}_2\text{H}_5\text{OOC}-\text{C}\qquad\qquad\text{CH}-\text{COOC}_2\text{H}_5\;\rightarrow\\
|\qquad\qquad\qquad\;\|\\
\text{CH}_3-\text{C}\qquad\qquad\text{C}-\text{CH}_3\\
\|\qquad\qquad\quad|\\
\text{O}\qquad\qquad\text{H}_2\text{N}\\
\text{IV}\qquad\qquad\qquad\text{X}
\end{array}
$$

$$
\begin{array}{c}
\text{R}\qquad\qquad\qquad\qquad\qquad\qquad\text{R}\\
|\qquad\qquad\qquad\qquad\qquad\qquad\;|\\
\text{CH}\qquad\qquad\qquad\qquad\qquad\;\;\text{CH}\\
\diagup\;\diagdown\qquad\qquad\qquad\qquad\diagup\;\diagdown\\
\text{C}_2\text{H}_5\text{OOC}-\text{CH}\quad\text{C}-\text{COOC}_2\text{H}_5\;\rightarrow\;\text{C}_2\text{H}_5\text{OOC}-\text{C}\quad\text{C}-\text{COOC}_2\text{H}_5\\
|\qquad\quad\|\qquad\qquad\qquad\qquad\;\|\qquad\;\|\\
\text{CH}_3-\text{C}\quad\text{C}-\text{CH}_3\qquad\qquad\;\text{CH}_3-\text{C}\quad\text{C}-\text{CH}_3\\
\|\quad\;|\qquad\qquad\qquad\qquad\qquad|\quad\;|\\
\text{O}\quad\text{N}\qquad\qquad\qquad\qquad\qquad\text{OH}\;\text{NH}_2\\
\qquad\text{H}_2\\
\text{XI}\qquad\qquad\qquad\qquad\qquad\qquad\text{XII}
\end{array}
$$

$$
\begin{array}{c}
\text{R}\\
|\\
\text{CH}\\
\diagup\;\diagdown\\
-\text{H}_2\text{O}\quad\text{C}_2\text{H}_5\text{OOC}-\text{C}\quad\text{C}-\text{COOC}_2\text{H}_5\\
\|\quad\;\|\qquad\qquad\qquad(6b)\\
\text{CH}_3-\text{C}\quad\text{C}-\text{CH}_3\\
\diagdown\;\diagup\\
\text{NH}\\
\text{VII}
\end{array}
$$
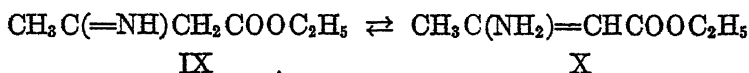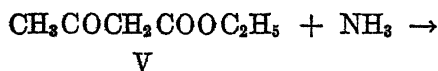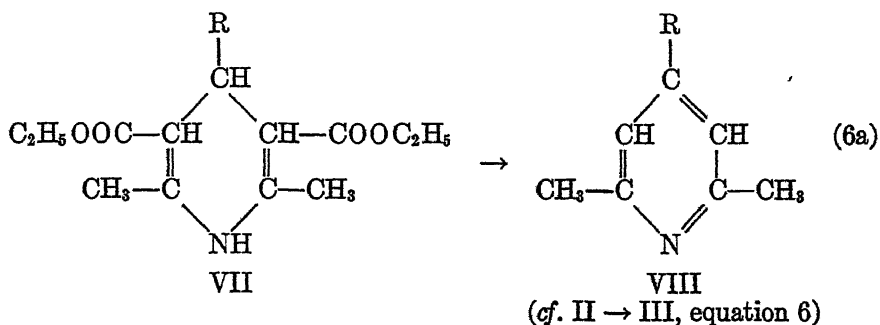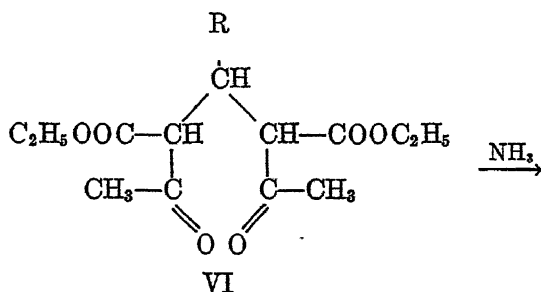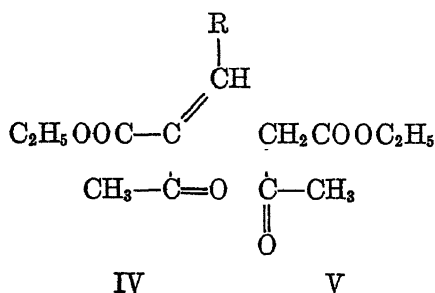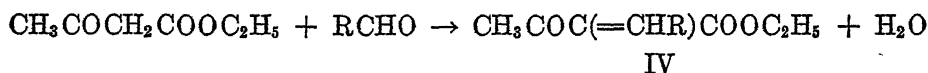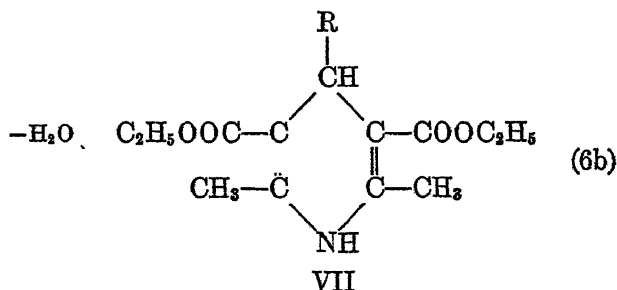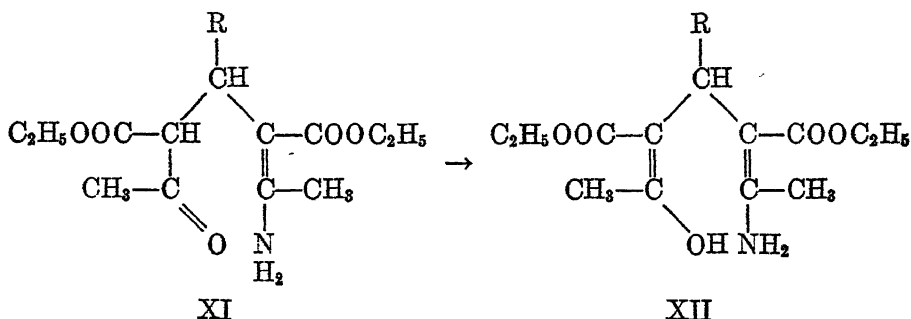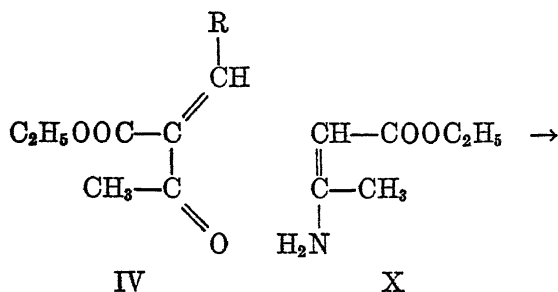
VII → VIII, as above (equation 6a) (68, 478, 478e)

It will be seen that these proposed mechanisms are the same in principle, but differ in the order of the assumed steps. In accordance with equation 6a, an alkylidene or arylidene bisacetoacetic ester (IV) is first formed, probably by the addition of a molecule of acetoacetic ester (V) to the carbon–carbon double bond of IV. Reactions of this type have of course been the subject of extensive investigation (Michael reaction: recent references, 603a; see also 697e). Equation 6b represents the formation of a partially ammonolyzed alkylidene or arylidene bisacetoacetic ester (XI) by addition (173a) of β-aminocrotonic ester (X) to an alkylidene or arylidene acetoacetic ester (IV). Ammonolysis—externally, as in equation 6a by ammonia itself, or intramolecularly, as in equation 6b by a substituted ammonia—results in ring closure and the formation of a dihydropyridine (VII).

The Hantzsch synthesis has been successfully carried out by heating β-aminocrotonic esters with alkylidene or arylidene bisacetoacetic esters in the

manner of equation 6b (478, 478e). However, several investigators (697d) have recorded failure to prepare dihydropyridines by the ammonolysis of alkylidene or arylidene bisacetoacetic esters (equation 6a), because, as Rabe and Elze (697c) have shown, the latter may instead undergo an intramolecular aldol condensation in accordance with the equation:

$$
\begin{array}{c}
\text{C}_6\text{H}_5 \\
| \\
\text{CH} \\
\diagup \quad \diagdown \\
\text{C}_2\text{H}_5\text{OOC}-\text{CH} \qquad \text{CHCOOC}_2\text{H}_5 \\
| \qquad\qquad | \\
\text{O}=\text{C} \qquad\quad \text{C}-\text{CH}_3 \\
\diagdown \qquad\quad || \\
\text{CH}_3 \quad\; \text{O}
\end{array}
\qquad \xrightarrow{\text{bases}}
$$

$$
\begin{array}{c}
\text{C}_6\text{H}_5 \\
| \\
\text{CH} \\
\diagup \quad \diagdown \\
\text{C}_2\text{H}_5\text{OOC}-\text{CH} \qquad \text{CHCOOC}_2\text{H}_5 \\
| \qquad\qquad |\diagup\text{CH}_3 \\
\text{O}=\text{C} \qquad\quad \text{C} \\
\diagdown \qquad\quad \diagdown \\
\text{CH}_2 \qquad \text{OH}
\end{array}
\qquad (6c)
$$
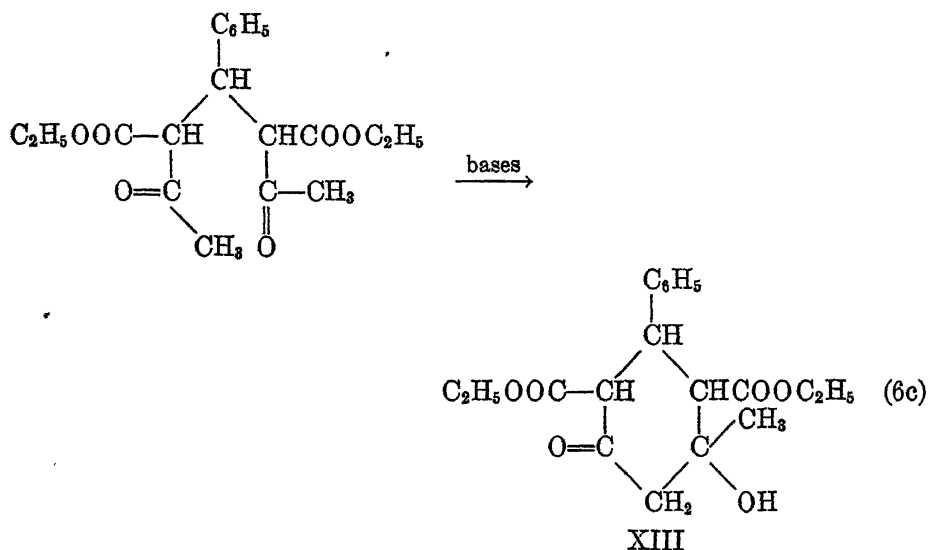
XIII

Loss of water from the aldol (XIII) gives a cyclohexene derivative representative of the type prepared by Knoevenagel (476b) by self-condensation of the same alkylidene or arylidene bisacetoacetic esters in the presence of a basic catalyst.

Some modifications of the Hantzsch synthesis, other than those mentioned above, are the following:

(a) Malonic esters react with β-aminocrotonic ester in the presence of alcoholic sodium ethylate to give dihydroxypyridine derivatives directly (478a, 478b, 480, 481a, 482; cf. 768a), as shown in the equation:

$$
\begin{array}{c}
\text{C}_2\text{H}_5\text{OOC} \\
\qquad\qquad\qquad \diagdown \\
\text{C}_2\text{H}_5\text{OOC}-\text{CH}_2 \qquad\qquad \text{CH} \\
| \qquad\qquad\qquad || \\
\text{O}=\text{C} \qquad\qquad\quad \text{C}-\text{CH}_3 \\
\diagdown \qquad\qquad\qquad | \\
\text{OC}_2\text{H}_5 \qquad\qquad \text{NH}_2
\end{array}
\qquad \xrightarrow[-2\text{C}_2\text{H}_5\text{OH}]{\text{C}_2\text{H}_5\text{ONa}}
$$

$$
\begin{array}{c}
\text{CO} \\
\diagup \quad \diagdown \\
\text{C}_2\text{H}_5\text{OOCCH} \qquad \text{CH} \\
| \qquad\qquad || \\
\text{OC} \qquad\quad \text{CCH}_3 \\
\diagdown \qquad \diagup \\
\text{NH}
\end{array}
\quad \rightleftharpoons \quad
\begin{array}{c}
\text{COH} \\
\diagup \quad \diagdown \\
\text{C}_2\text{H}_5\text{OOCC} \qquad \text{CH} \\
|| \qquad\qquad | \\
\text{HO}-\text{C} \qquad\quad \text{CCH}_3 \\
\diagdown \qquad \diagup \\
\text{N}
\end{array}
\qquad (6d)
$$
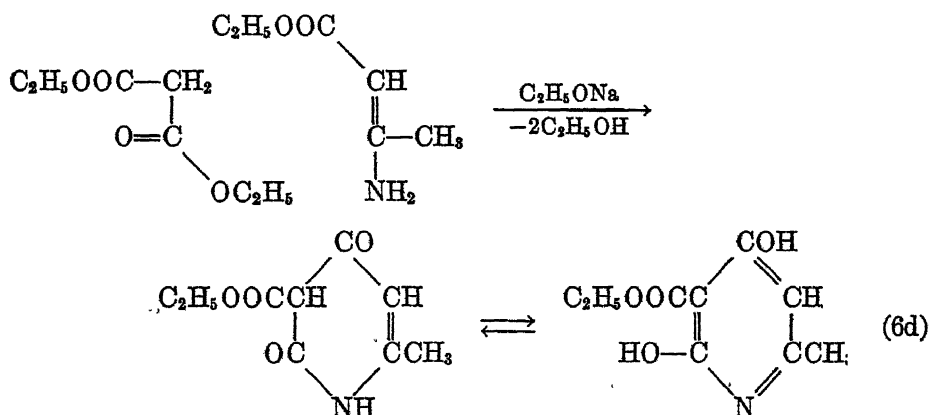
(b) Benary (43d) dissolved β-aminocrotonic ester and an equivalent of 1,2-dichloroethyl ether in benzene; a vigorous reaction occurred on short standing, to give the dihydropyridine derivative (XIV) below:

$$CH_2Cl$$
$$|$$
$$CH$$

$$C_2H_5OOC—C \qquad C—COOC_2H_5 \xrightarrow{HNO_3}$$

$$CH_3—C \qquad C—CH_3$$

$$NH$$

XIV

$$CH_2Cl$$
$$|$$
$$C$$

$$C_2H_5OOC—C \qquad C—COOC_2H_5 \qquad (6e)$$

$$CH_3—C \qquad C—CH_3$$

$$N$$

XV
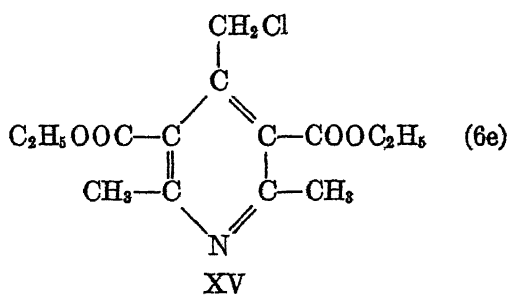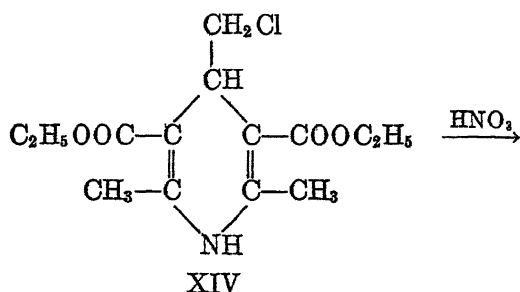
It is oxidized by dilute nitric acid to the corresponding pyridine (XV), which has a chlorine activated by carbonyl and carbimide groups (C=N) and therefore very mobile. The dichloroethyl ether has acted only as a source of mono-chloroacetaldehyde.

(c) Claisen (161b) obtained 2,6-dimethyl-3,5-diacetylpyridine (XVII) by ammonolysis of methenylbisacetylacetone (XVI):

$$CH_3C=O \quad COCH_3$$
$$| \qquad |$$
$$CH_3CO—C \qquad CH—COCH_3 \quad \rightleftarrows$$
$$CH$$

XVI

$$OH$$
$$|$$
$$CH_3C=O \quad C—CH_3$$
$$| \qquad ||$$
$$CH_3CO—C \qquad C—COCH_3 \quad NH_3$$
$$CH$$

$$N$$

$$CH_3—C \qquad C—CH_3$$
$$CH_3CO—C \qquad C—COCH_3 \qquad (6f)$$
$$CH$$

XVII
Diacetyllutidine
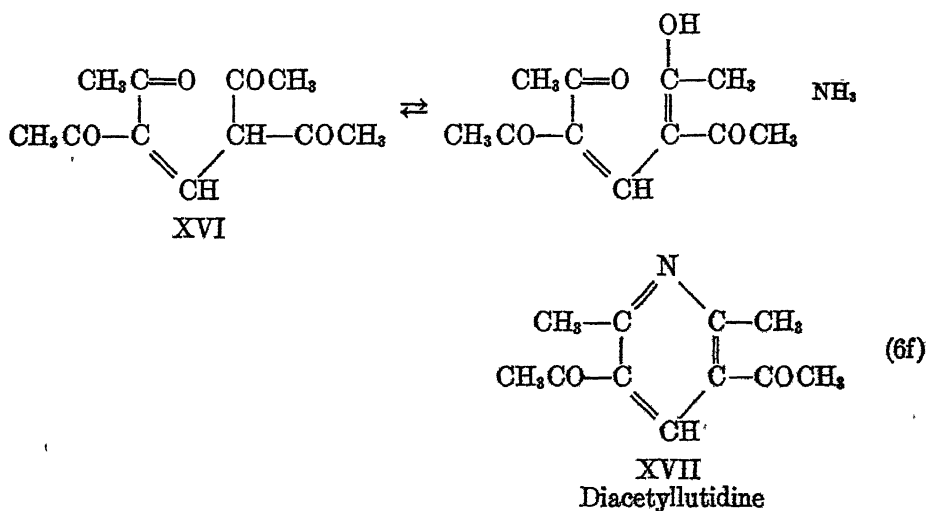
The methenylbisacetylacetone (XVI) was obtained by the action of the potassium salt of acetylacetone on ethoxymethyleneacetylacetone, which was, in turn, prepared from acetylacetone, ethyl orthoformate, and acetic anhydride.

It is worth while pointing out that aldehydes and ketones are often very readily ammonolyzed—either by ammonia itself, or by a substituted ammonia. In many cases, these reactions can lead to ring closure, as in the pyridine syntheses under discussion. While esters ammonolyze fairly readily (see Claisen's reaction (6d) above), acids do so with some difficulty. Cyclization rarely takes place because of an intramolecular ammonolysis that involves an alcoholic hydroxyl, RCH_2OH.

The fine details of the action of ammonia or a substituted ammonia on the carbonyl group are unknown; it is not necessary to assume that enolization precedes ammonolysis, as has been done in equations 6b and 6f. Perhaps an addition to the carbonyl group is followed by loss of water, in the sense of the equation below:

$$
\begin{array}{l}
-\overset{|}{C}H \\
\,\,\,| \\
-C=O
\end{array}
+ H_2N-\overset{\|}{C}- \longrightarrow
\begin{array}{c}
-\overset{|}{C}H\ OH \\
\diagdown\,\diagup \\
-C\qquad\overset{\|}{C}- \\
\diagdown\,\diagup \\
NH
\end{array}
\xrightarrow{-H_2O}
\begin{array}{c}
-\overset{|}{C} \\
\diagdown \\
-\overset{\|}{C}\qquad\overset{\|}{C}- \\
\diagdown\,\diagup \\
NH
\end{array}
\quad (6g)
$$
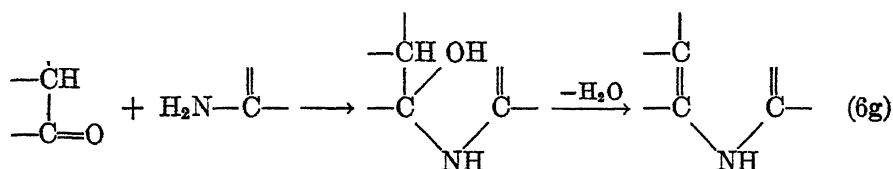
The effect of different groups on the ring closure of the Hantzsch synthesis has been investigated by Hinkel, Ayling, Morgan, and Cremer (426).

(5) Pyridine derivatives may be formed directly by heating 1,5-diketones with hydroxylamine (476a), as Knoevenagel has shown in the two examples below:

$$
\begin{array}{c}
C_6H_5 \\
| \\
C \\
\diagdown \\
C_2H_5OOC-C \qquad C-COOC_2H_5 \\
\parallel \\
C_6H_5-C \qquad C-C_6H_5 \\
\diagdown \quad \diagup \\
N
\end{array}
\qquad (7)
$$

III
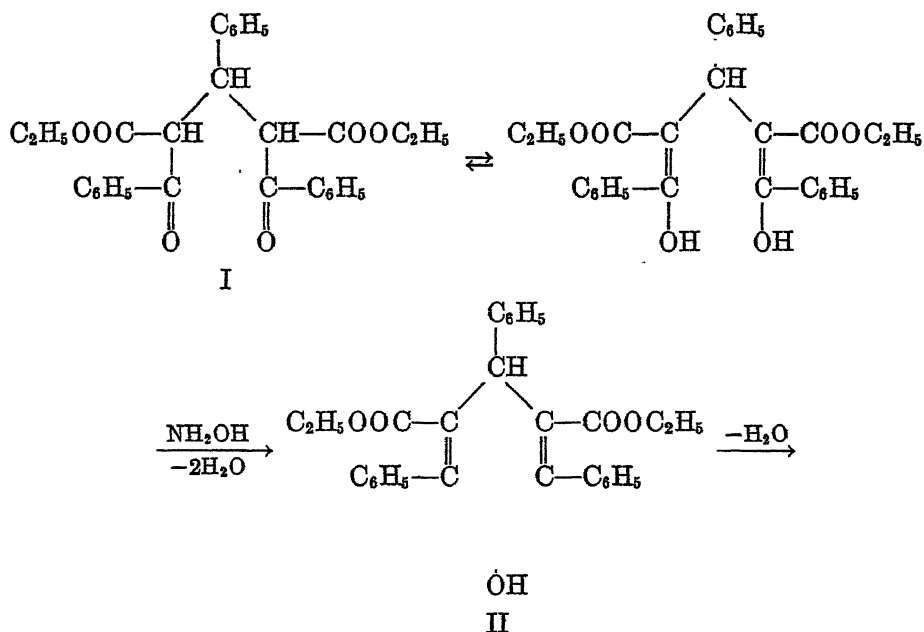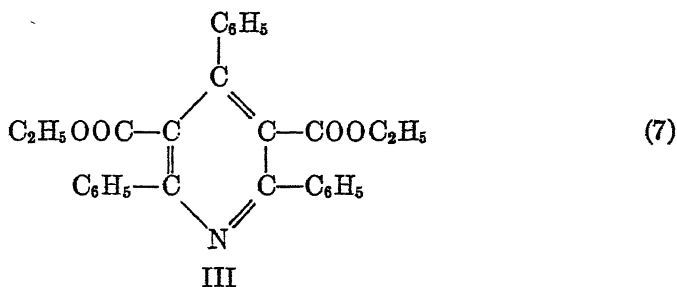
The ethyl ester of 2,4,6-triphenylpyridine-3,5-dicarboxylic acid (III) is formed by heating benzylidenedibenzoylacetic ester (I) with aqueous hydroxylamine for 4 hr. at 120–130°C. It has been assumed, in accordance with the work of S. Skraup (763b), that there is formed an intermediate (II) with hydroxyl attached to nitrogen. 1,2,3,5-Tetraphenyl-1,5-pentanedione (IV) is converted to tetraphenylpyridine (V) by the action of hydroxylamine hydrochloride at 140–150°C. (477).

$$
\begin{array}{cc}
\begin{array}{c}
C_6H_5 \\
| \\
CH_2-C\!=\!O \\
C_6H_5-CH \\
\diagdown \\
CH-C\!=\!O \\
\diagup \qquad | \\
C_6H_5 \quad C_6H_5
\end{array}
& + \; NH_2OH \rightarrow 3H_2O +
\begin{array}{c}
C_6H_5 \\
| \\
CH-C \\
\diagdown \\
C_6H_5-C \qquad N \\
\diagdown \quad \diagup \\
C\!=\!C \\
| \qquad | \\
C_6H_5 \quad C_6H_5
\end{array}
\end{array}
\qquad (8)
$$

IV   V
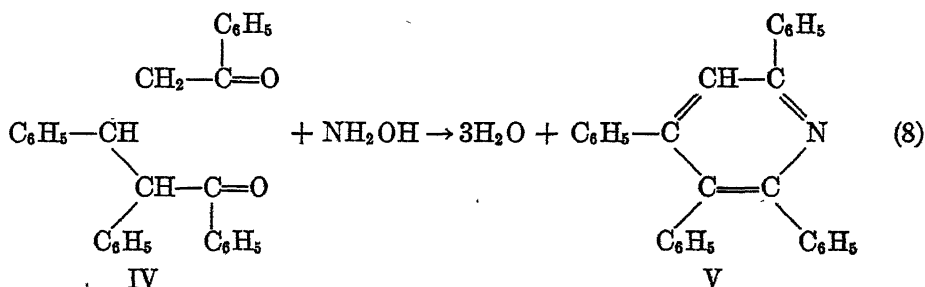
The applicability of this synthesis is rather limited.

A somewhat related reaction is the formation, in 25 per cent yield, of 2-methyl-6-phenylpyridine by the dry distillation of the oxime of cinnamylideneacetone (750).

$$
\begin{array}{cc}
\begin{array}{c}
CH\!\!-\!\!-CH\!=\!CH \\
\parallel \qquad \qquad | \\
C_6H_5-CH \quad HON\!=\!C-CH_3
\end{array}
& \xrightarrow{-H_2O}
\begin{array}{c}
CH \\
\diagup \; \diagdown \\
HC \qquad CH \\
\parallel \qquad | \\
C_6H_5C \qquad CCH_3 \\
\diagdown \; \diagup \\
N
\end{array}
\end{array}
\qquad (8a)
$$

2-Methyl-6-phenylpyridine
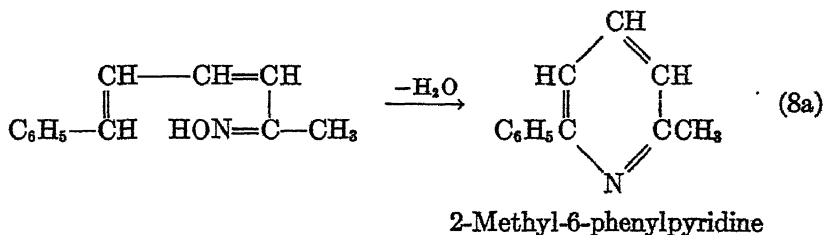
(6) Aliphatic aldehydes, when heated with ammonia, form a mixture of pyridine homologues. There are many ways in which these reactions may be carried out.

(a) When acetaldehyde-ammonia is heated for 12 hr. with double its volume of absolute alcohol at 120–130°C., there is formed 2-methyl-5-ethylpyridine (aldehyde collidine), together with other bases (2).

(b) Pläth (691), Chichibabin (119), Chichibabin and Oparina (150), and

others heated aldehyde-ammonia, or paraldehyde, with ammonia to temperatures of 200°C. and above, obtaining aldehyde collidine in yields of 50 per cent of the theoretical or over. At the same time, smaller amounts of 2- and 4-methylpyridines and β-collidine (4-methyl-3-ethylpyridine) were formed (20, 119, 150, 263, 489, 691; cf. 151).

Similar heating of propionaldehyde with ammonia at 205–210°C. (263a), or with ammonia in the presence of aluminum trioxide at 310–320°C. (151), gave 2-ethyl-3, 5-dimethylpyridine, 3,5-dimethylpyridine, and 3,5-dimethyl-4-ethylpyridine.

(c) Several patents have been granted for the preparation of aldehyde collidine by heating paraldehyde with aqueous ammonia; yields of crude base up to 80 per cent of the theoretical are claimed (378).

(d) Mixed pyridine bases may be formed by passing aldehydes and ammonia over a contact catalyst, such as alumina (130, 136, 146, 148, 151, 661). Pyridine itself may be made, though in poor yield, by passing ammonia, acetaldehyde, and acrolein over heated alumina (152).

Chichibabin has discussed the mechanism of these reactions in a recent article which is not available because of conditions imposed by the war (120; see also 123 and 119).

Strain (784) is of the opinion that the formation of 2-methylpyridine and aldehyde collidine is best explained by assuming a series of aldol condensations, followed by a cyclization and dehydrogenation in the sense of the equations below:

$$CH_3CHO + NH_3 = H_2O + CH_3CH{=}NH$$

<p style="text-align:center">I</p>

$$3CH_3CH{=}NH \longrightarrow \begin{array}{c} CH_3\,CHNH_2 \\ | \\ CH_2\,CHNH_2 \\ | \\ {*}CH_2CH{=}NH \end{array}$$

<p style="text-align:center">II</p>

(9)

<p style="text-align:center">II   III   IV
2-Methylpyridine</p>

To explain the formation of aldehyde collidine (VII), it may be assumed that acetaldehyde undergoes a Claisen reaction with the trialdol (II) at the point indicated by the asterisk, to form V.

$$V \qquad\qquad VI \qquad\qquad VII$$
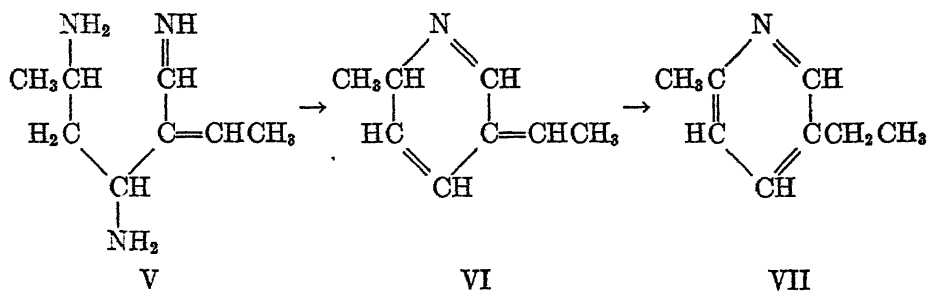
The grouping —CH_2CH=NH— is present in an ammono aldehyde alcohol or ammono aldehyde ether, and the hydrogens of the methylene group will be reactive in the sense that the alpha hydrogens of an aldehyde or ketone are reactive. The acetaldehyde may of course condense with the dihydropyridine derivative (III) to form VII.

The investigations of Sherlin (759a), Alder (7a, 7b, 7c), and coworkers suggest another manner in which aldehydes and ketones may be converted to pyridine derivatives. Normally, an α,β-unsaturated aldehyde or ketone will readily undergo an extensive polymerization, but this may be limited to the first stage by adding an inhibitor, hydroquinone. Under these circumstances a dimer may be isolated. According to Alder (7b), the reaction always follows the course (a) of the equation below:

$$VII \qquad\qquad VIII \qquad\qquad IX \qquad\qquad (9a)$$
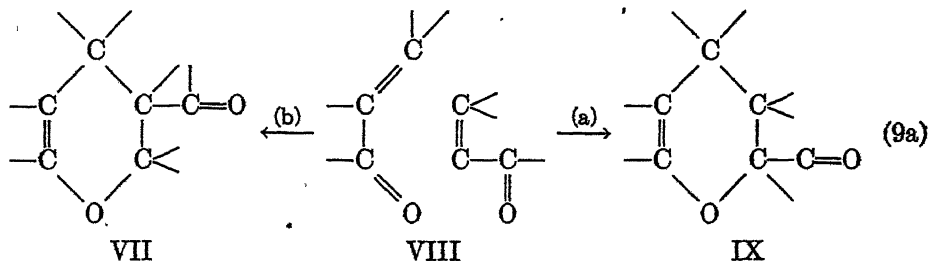
Acrolein and crotonaldehyde thus give X and XI, respectively, although Sherlin (probably erroneously) considers that the dimer of the former is XII.

$$X \qquad\qquad XI \qquad\qquad XII$$
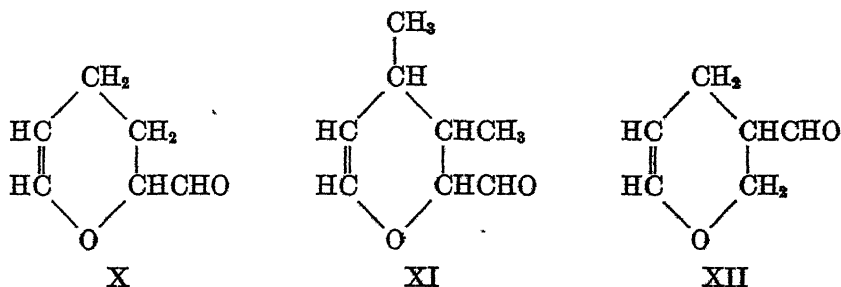
The heterocyclic oxygen of VII, IX, X, XI, or XII can be replaced by an —NH group by the action of ammonia, as is the case in the pyrone series (Section II,

B, (2)), but undoubtedly with more difficulty and at a higher temperature, since the ring closure of the hypothetical intermediate

$$
\begin{array}{ccc}
 & CH_2 & \\
HC & & CH_2 \\
\| & & | \\
HC & & CHCHO \\
NH_2 & & OH
\end{array}
$$
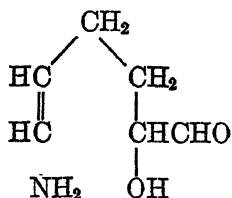
will involve the loss of water from an alcoholic hydroxyl. Acrolein-ammonia, $C_6H_9ON \cdot 0.5H_2O$, may have a structure corresponding to either X or XII, with —NH— replacing the heterocyclic oxygen (cf. 162a). If the formula resembles XII, an intramolecular oxidation–reduction (ring → aromatic, —CHO → CH₃) would give the β-methylpyridine which is known to be the principal product formed when acrolein-ammonia is heated (26a, 162a), or when glycerol is heated with ammonium phosphate (779a). By-products of the reaction are reported to be 3-ethylpyridine, 3-propylpyridine, pyridine, and small quantities of 2-substituted pyridines (2-picoline, etc.) (779a).

It is interesting that Delépine and Horeau (235a) have obtained a dimeric crotonaldehyde of the structure below (XIII), by treating crotonaldehyde with hydrochloric acid.

$$
\begin{array}{ccc}
 & CH & \\
H_2C & & CCHO \\
| & & | \\
CH_3CH & & CHCH_3 \\
 & O &
\end{array}
$$

XIII
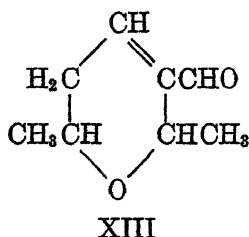
A molecular rearrangement must have occurred at some stage of its formation, if this formula is correct. It is entirely reasonable to suppose that the reactions between ammonia and aldehydes to give pyridine derivatives are also complicated by molecular rearrangements that may occur in an intermediate step. A good discussion of the mechanism is given by Chichibabin (119, 120, 123).

(7) Acetylene, when heated with ammonia in the presence of a contact catalyst (alumina, carbides of iron, aluminum, chromium, tungsten, and uranium, etc.) at about 250°C. and 50 atmospheres, gives acetonitrile, together with a quantity of mixed pyridine bases and very small amounts of pyrroles (126, 144, 145, 745a). It is known that acetaldehyde is formed by the catalytic hydration of acetylene in dilute sulfuric acid with mercuric salts as catalysts; one may speculate and say that the approximate ammonia system equivalent of acetaldehyde, ethylidenimine, $CH_3CH=NH$ (an ammono aldehyde alcohol), is an intermediate in these reactions. Dehydrogenation would give an acid anammonide, acetonitrile,

CH₃CN, while condensation in the manner of method (6) above would give pyridine bases. - Many patents have been granted on this method (660).

(8) Alkylpyridinium halides, when heated to temperatures not far removed from 300°C., give mixtures of the hydrohalides of 2- and 4-alkylpyridines. Ladenburg, the originator of this synthesis, thus prepared (among other compounds) 2- and 4-ethylpyridines and 2,4-diethylpyridine by heating pyridine ethiodide in sealed tubes (551). Chichibabin (111) records that a small amount of β-ethylpyridine is also formed. Obviously, the Ladenburg rearrangement offers a rather inconvenient way of preparing pure homologues of pyridine. Nevertheless, the method seems to have been used a number of times for making 2- and 4-benzylpyridines, with copper bronze as a catalyst (157, 630a, 553; cf. 124). A small amount of 3-benzylpyridine is also formed (111).

(9) Yields of 2-, 3-, and 4-substituted pyridines totalling 70–80 per cent of the theoretical are formed from aryldiazonium salts and pyridine at temperatures up to 70°C. (129, 129a, 171a, 414). As an example, a mixture of the three p-nitrophenylpyridines is formed by adding 435 parts of an aqueous acid solution of p-nitrobenzenediazonium chloride to 500 parts of pyridine, stirring during 3 hr. at 24–26°C., pouring into water, and filtering. The mechanism of this rather interesting reaction is not known, but it is presumably similar to that of the synthesis of diphenyl derivatives from diazonium salts and benzene hydrocarbons in alkaline solution (376a).

C. RING OPENINGS

The pyridine nucleus is normally difficult to rupture. Oxidation of quinoline (benzopyridine) gives pyridine-2,3-dicarboxylic acid (quinolinic acid) with destruction of the benzene ring. Determination of nitrogen in pyridine derivatives by the usual Kjeldahl method is apt to lead to low results because of incomplete destruction of the pyridine ring.

There are, however, many methods of opening the ring that depend as a general rule upon the decomposition of quaternary salts of pyridine by means of alkalies, amines, or other bases. The reaction of Bucherer and Schenkel (103) does not follow this scheme, since pyridine is first heated with sodium bisulfite to form the addition compound, C₅H₅N·3NaHSO₃, which is split by alkali into the sodium salt of glutacondialdehyde, NaOCH=CHCH=CHCHO, ammonia, and sodium sulfite.

(a) Pyridine and 2,4-dinitrochlorobenzene react when heated to give a quaternary ammonium salt, 2,4-dinitrophenylpyridinium chloride (cation = I) which undergoes ring cleavage in the presence of alkali to form a red compound (III) as an intermediate. Dilute hydrochloric acid hydrolyzes it to dinitroaniline (V) and glutacondialdehyde (IV), which is isolated as the product of its reaction with aniline, glutacondialdehyde anil anilide hydrochloride (VI). It is interesting that in the absence of water in glacial acetic acid solution, hydrochloric acid converts III to dinitrophenylpyridinium chloride (I). The equations follow.

$$
\begin{array}{ccc}
\text{I} & \text{II} & \text{III}
\end{array}
$$

Structure I:
```
        CH
       /  ‖
     HC    CH
     ‖      |
     HC    CH
       \  //
        N+
        |
   (benzene ring) NO2
        |
       NO2
```
$\xrightarrow{OH^-}$

Structure II:
```
        CH
       /  ‖
     HC    CH
     ‖      |
     HC    CHOH
       \  /
        N
        |
   (benzene ring) NO2
        |
       NO2
```
$\longrightarrow$

Structure III:
```
        CH
       /  ‖
     HC    CH
     ‖      |
     HC    CHO
       \
        NH
        |
   (benzene ring) NO2
        |
       NO2
```
$\rightleftharpoons$

I — II — III

Structure IV (left, reactant):
```
        CH
       //  ‖
     HC    CH
     |      ‖
     HC    CHOH
       \\
        N
        |
   (benzene ring) NO2
        |
       NO2
```
$\xrightarrow[+H_2O]{\text{dilute HCl}}$

Structure IV:
```
        CH
       /  ‖
     HC    CH
     ‖      |
     HC    CHO
     |
     OH
```

$+$

Structure V:
```
        NH2
   (benzene ring) NO2
        |
       NO2
```

(10)

$$
IV + 2C_6H_5NH_2 \cdot HCl = C_6H_5NHCH \qquad CH = NC_6H_5 \cdot HCl + HCl
$$

Structure VI:
```
        CH
       /  ‖
     CH    CH
     ‖      |
```
VI

The intermediate (II), which has not been isolated, has been added for purposes of explanation; it is formed by the attack of the hydroxyl ion of the alkali upon the 2-carbon atom of the pyridine ring, and belongs to the class of pseudo bases (Section II, I, 7) or ammono aquo meroacetals. The enol form of III will be at least partly converted to a salt ($=CHOH \rightarrow =CHO^- Na^+$) in alkaline solution. It will be noted that resonance will allow the anionic charge to appear upon the nitrogen attached to position 1 of the benzene ring, or upon the oxygen atoms of the two nitro groups, thereby accounting for the stability and for the red color observed. As extensive a resonance is not possible with the cyclic form (II), as might have been inferred from the fact that the simple pseudo bases of the pyridine and quinoline series are colorless. However, the pseudo base from 2,4-dinitrophenylisoquinolinium chloride is red (Section V, G, 1).

The two tautomeric forms of III may be represented by the partial formulas below, which represent, respectively, an ammono enol (or, better, an ammono enol ether) and an ammono aldehyde ether or Schiff base. The latter, as is well

$$
-CH = CH - NHC_6H_4(NO_2)_2 \qquad = CH - CH = NC_6H_4(NO_2)_2
$$

known, may be readily hydrolyzed by acids (702c); that the former behave similarly follows from the work of Mannich and his students (575), who find that the ammono enol ether, or enamine, N-butenylpiperidine (VII), is readily hydrolyzed in accordance with the equation,

$$CH_3 CH_2 CH=CH \cdot NC_5 H_{10} + HOH \xrightarrow{acids} C_5 H_{10} NH \cdot HX +$$
$$\text{VII}$$

$$CH_3 CH_2 CH=CHOH \rightarrow C_5 H_{10} NH \cdot HX + CH_3 CH_2 CH_2 CHO \quad (11)$$
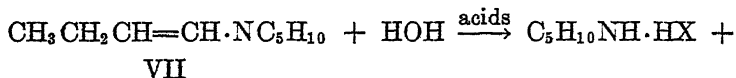
The related water system compounds, vinyl ethyl ether (286a, 816), $CH_2=CHOC_2 H_5$, and α-methoxystyrene (630), $C_6 H_5 C(OCH_3)=CH_2$, are easily hydrolyzed by acids, the former even at room temperatures, to give acetaldehyde and acetophenone, respectively, together with ethyl and methyl alcohols. Ethyl styryl ether, $C_6 H_5 CH=CHOC_2 H_5$, is converted to ethanol and phenylacetaldehyde by boiling with dilute sulfuric acid (638). Enamines of the general formula $RCH(NR_2)CH=CHNR_2'$ are hydrolyzed under acid conditions in a similar manner (575, 577, 579, 580, 601c).

Meyer and coworkers (601b, 601c, 601d) have given other examples of the reactivity of compounds with an amino or substituted amino group directly attached to a doubly bound carbon atom.

All in all, the net result of these transformations is the hydrolysis of pyridine to glutacondialdehyde and ammonia, a reaction that is in effect a reversal of its synthesis (see method (1), Section II, B). The reaction has been fully investigated by Zincke and his coworkers (709, 833, 834, 835, 836, 838, 840). W. König has observed that a similar ring opening occurs when p-nitrophenylpyridinium chloride is boiled with alkali (510; cf. 515).

Pyridine methiodide, when treated with alkali, gives a mixture of N-methylpyridinium hydroxide and 1-methyl-2-hydroxy-1,2-dihydropyridine, with the equilibrium favoring the former. Nevertheless, Decker and Kaufmann (217) have observed that some methylamine is formed by boiling pyridine methiodide with 10 per cent sodium hydroxide solution, indicating that ring opening has taken place to some extent.

(b) Ring openings have been observed when alkali reacts with quaternary pyridinium salts formed from sulfur trioxide (pyridine-N-sulfonic acid (37, 38)), cyanogen bromide (508, 515), chlorosulfonic acid ethyl ester (36), phosphorus pentachloride, benzanilidenimidochloride, and others (710).

(c) Freytag (345) and coworkers discovered in 1932 that pyridine slowly turns yellow in ultraviolet light, particularly at wave lengths of 248–266 millimicrons. Paper impregnated with pyridine and then exposed to ultraviolet light gave with primary amines characteristic colors which serve as a test not only for the amines in question but also for pyridine. Some pyridine derivatives undergo this reaction (e.g., 3-aminopyridine, particularly at 313 millimicrons), while others do not or do so slowly (2-aminopyridine, 2, 4, 6-trimethylpyridine). It was shown definitely that the pyridine ring was opened to form the enol of glutacondialdehyde, or a substitution product, which reacted with the primary aromatic amines to give the colors observed.

(d) König (513) believes that the products of the action of alcohol upon some pseudo bases of the pyridine series have open-chain formulas.

$$
\begin{array}{c}
\text{CH} \\
\text{HC} \diagup \diagdown \text{CH} \\
\text{HC} \quad \text{CHOH} \\
\diagdown \diagup \\
\text{N} \\
\text{R}
\end{array}
\;+\; \text{R'OH} \;\rightarrow\;
\begin{array}{c}
\text{CH} \\
\text{HC} \diagup \diagdown \text{CH} \quad \text{OH} \\
\text{HC} \quad \text{CH} \\
\diagdown \diagup \diagdown \\
\text{NR} \quad \text{OR'} \\
\text{H}
\end{array}
\qquad (12)
$$
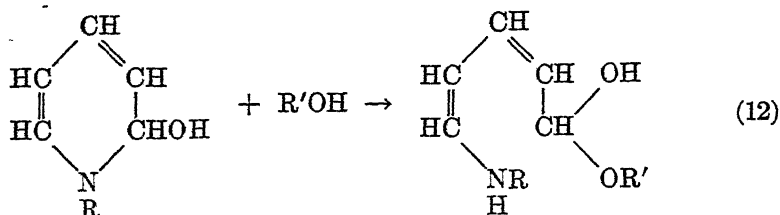
R' is an alkyl group.

(e) Shaw (756) finds that little if any piperidine is formed when pyridine is reduced by sodium in boiling 95 per cent alcohol; ammonia is evolved·and the main product is a nitrogen-free resin. The ring fission takes place at the 1,4-dihydro stage of the reduction and does not appear to occur to any extent in absolute alcohol, as piperidine is formed in good yield. The following experiment is described by Shaw (757): When a solution of 80 g. of pyridine in 400 cc. of boiling 95 per cent alcohol was treated with sodium (24 g.), no ammonia was evolved. Hydroxylamine hydrochloride (36 g.) in dry alcohol was added and the mixture boiled for a few minutes, whereupon ammonia was evolved copiously. From this solution, 28 g. of the oxime of glutardialdehyde was obtained, or 65 per cent, calculated on the basis of the hydroxylamine.

A similar reduction of 2-stilbazole ($C_5H_4NCH{=}CHC_6H_5{-}2$) gives β-phenethyltetrahydropyran (a ring opening, followed by a ring closure) (756, first reference).

(f) Partially hydrogenated pyridine derivatives often undergo ring cleavage rather readily. 1,4,5,6-Tetrahydro-2-methylpyridine (I) thus reacts with nitrous acid to form acetylbutyl alcohol (II), as represented by the following equation (86, 565, 626):

$$
\begin{array}{c}
\text{CH}_2 \\
\text{H}_2\text{C} \diagup \diagdown \text{CH} \\
\text{H}_2\text{C} \quad \text{CCH}_3 \\
\diagdown \diagup \\
\text{NH} \\
\text{I}
\end{array}
\;+\text{HONO}\;
\begin{array}{c}
\text{CH}_2 \\
\text{H}_2\text{C} \diagup \diagdown \text{CH}_2 \\
\text{HOCH}_2 \quad \text{COCH}_3 \\
\\
\text{II}
\end{array}
\qquad (13)
$$
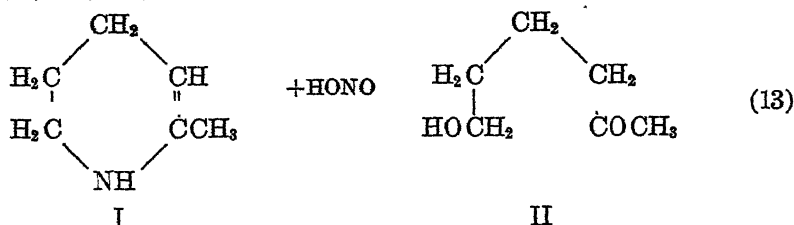
The ring may also be opened by benzoyl chloride, in the manner of the equation below:

$$
\text{I} + \text{C}_6\text{H}_5\text{COCl} \rightarrow
\begin{array}{c}
\text{CH}_2 \\
\text{H}_2\text{C} \diagup \diagdown \text{CH} \\
\text{H}_2\text{C} \quad \text{CCH}_3 \\
\diagdown \diagup \\
\text{N} \\
\text{COC}_6\text{H}_5
\end{array}
\quad \text{H}_2\text{O}
$$

$$
\begin{array}{c}
\text{CH}_2 \\
\diagup \quad \diagdown \\
\text{H}_2\text{C} \qquad \text{CH} \\
| \qquad\quad || \\
\text{H}_2\text{C} \qquad \text{COH} \qquad \text{CH}_3\text{CO(CH}_2)_4\text{NHCOC}_6\text{H}_5 \quad (14) \\
| \qquad\quad | \\
\text{NH} \qquad \text{CH}_3 \\
| \\
\text{COC}_6\text{H}_5
\end{array}
$$
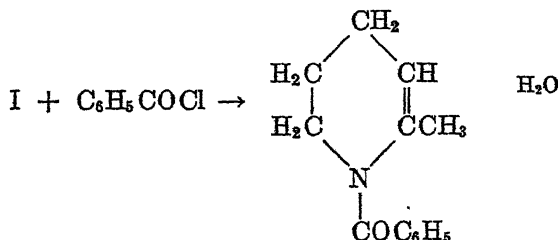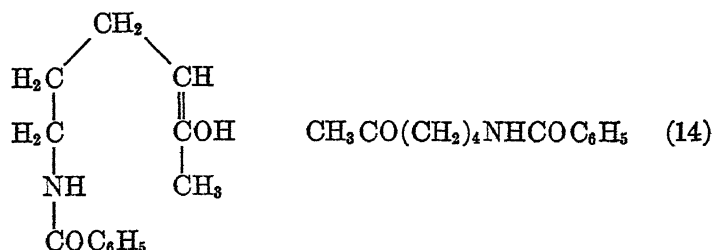
The tetrahydromethylpyridine above (I) is an ammono enol ether, because of the grouping —CH=C(CH₃)—NH—, and is easily hydrolyzed, as are the related compounds of Zincke (see Section II, C, (a)). The reactions of equations 13 and 14 may be remembered by assuming a reaction of I with water to give 6-amino-2-hexanone (III).

$$
\begin{array}{ccc}
\begin{array}{c}
\text{CH}_2 \\
\diagup \quad \diagdown \\
\text{CH}_2 \qquad \text{CH} \\
| \qquad\quad || \\
\text{CH}_2 \qquad \text{COH} \\
| \qquad\quad | \\
\text{NH}_2 \qquad \text{CH}_3
\end{array}
& \rightleftarrows &
\begin{array}{c}
\text{CH}_2 \\
\diagup \quad \diagdown \\
\text{CH}_2 \qquad \text{CH}_2 \\
| \qquad\quad | \\
\text{CH}_2 \qquad \text{COCH}_3 \\
| \\
\text{NH}_2
\end{array}
\\
& \text{III} &
\end{array}
$$
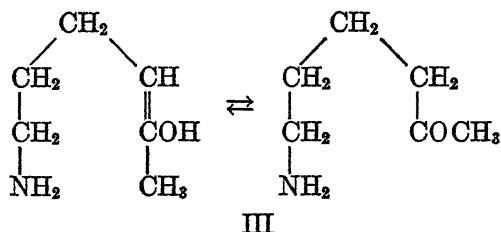
The reaction of III with nitrous acid will give the ketone alcohol (II), while reaction with benzoyl chloride will give a benzoyl derivative of III, as shown in equation 14. The conversion of I to III is the hydrolysis of an ammono enol ether to an ammono alcohol-aquo ketone or its enol.

(g) Ring scission has often been noticed with the 1,4-dihydropyridines obtained as intermediates in the Hantzsch synthesis (405, 483, 476, 743, 763; see Section II, B). That 1,4-dihydropyridine itself may readily be converted to the open-chain glutardialdehyde dioxime has been shown by the work of Shaw, which was discussed in section II, C, (e). 1,4-Dihydropyridine is a partial anammonide of an ammono dienol, as may be seen from the scheme below; no strictly analogous derivatives of the water system exist.

$$
\begin{array}{ccc}
\begin{array}{c}
\quad\text{CH}_2\text{CHO} \\
\diagup \\
\text{CH}_2 \\
\diagdown \\
\quad\text{CH}_2\text{CHO} \\
\text{IV}
\end{array}
&
\begin{array}{c}
\text{CH}=\text{CHOH} \\
\diagup \\
\text{CH}_2 \\
\diagdown \\
\text{CH}=\text{CHOH} \\
\text{V}
\end{array}
&
\begin{array}{c}
\text{CH}=\text{CHNH}_2 \\
\diagup \\
\text{CH}_2 \\
\diagdown \\
\text{CH}=\text{CHNH}_2 \\
\text{VI}
\end{array}
\end{array}
$$

$$
\begin{array}{cc}
\begin{array}{c}
\text{CH}=\text{CH} \\
\diagup \quad\quad \diagdown \\
\text{CH}_2 \qquad\quad \text{NH} \\
\diagdown \quad\quad \diagup \\
\text{CH}=\text{CH} \\
\text{VII}
\end{array}
&
\begin{array}{c}
\text{CH}_2\text{CH}=\text{NOH} \\
\diagup \\
\text{CH}_2 \\
\diagdown \\
\text{CH}_2\text{CH}=\text{NOH} \\
\text{VIII}
\end{array}
\end{array}
$$
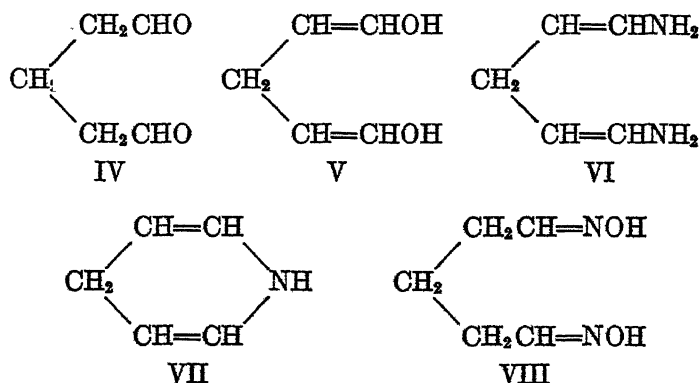
Glutardialdehyde (IV) is tautomeric with the dienol form (V). The corresponding (hypothetical) ammono dienol is VI, and its anammonide, 1,4-dihydropyridine, is VII; because of the hydrogen attached to nitrogen it still should have the properties of an enol. This fact, coupled with the diminished resonance of a six-membered ring with two isolated double bonds, is responsible for the ready formation of glutardialdoxime (VIII) by reaction with hydroxylamine. Pyrrole

$$CH=CH$$
$$| \qquad \backslash$$
$$| \qquad \qquad NH$$
$$| \qquad /$$
$$CH=CH$$
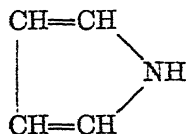
is closely related to 1,4-dihydropyridine, but it is not as reactive because of an increase in the resonance energy.

D. REDUCTION OF PYRIDINE BASES

Complete reduction of pyridine, either by sodium in absolute alcohol or by hydrogen in the presence of a catalyst (262, 588, 651, 736, 737a) or electrolytically (5, 262) gives piperidine,

$$CH_2{-}CH_2$$
$$CH_2 \qquad NH$$
$$CH_2{-}CH_2$$
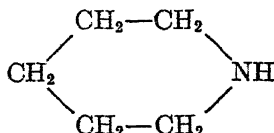
a saturated ammono alcohol. Partial reduction of pyridine to dihydro and tetra-hydro derivatives has been accomplished (see Section II, C, (e); cf. 494, 738), but no attempt will be made to cover the literature on this subject.

Metallic sodium, potassium, and lithium reduce pyridine (in the absence of other solvent) to alkali-metal substitution products of hydrogenated dipyridyls; when pyridine is oxidized with atmospheric oxygen at somewhat elevated temperatures, a mixture of dipyridyls is formed (11, 278, 659, 767a, 807a, 814a).

Sodium thus reacts with pyridine at room temperatures to form a greenish solution, from which a black-green substance of the composition $(C_5H_5N)_2Na$ can be isolated by removal of excess of pyridine in a vacuum. When this is heated in a vacuum at 130°C., monopyridine sodium, C_5H_5NNa, is formed, though this probably has double the formula indicated. Both substances are spontaneously inflammable in air, and when hydrolyzed with water (moist ether) give tetrahydrodipyridyls, which air oxidation converts to 4,4'-dipyridyl (II) with smaller amounts of the 2,2'-isomer. The reactions may be represented by the following equations:

$$
\begin{array}{c}
\text{CH}=\text{CH} \qquad \text{CH}=\text{CH} \\
\diagup \qquad \diagdown \qquad \diagup \qquad \diagdown \\
\text{N} \qquad \text{C}-\text{C} \qquad \text{N} \\
\diagdown \qquad \diagup \qquad \diagdown \qquad \diagup \\
\text{CH}-\text{CH} \qquad \text{CH}-\text{CH} \\
\text{II}
\end{array} \tag{15}
$$
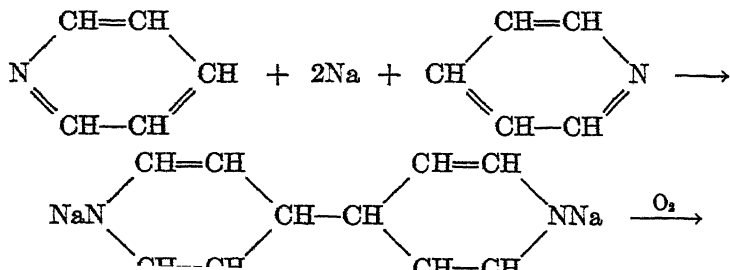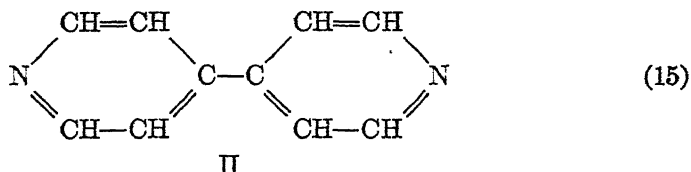
2,2'-Dipyridyl is formed similarly. If sodium in a large excess of pyridine is heated for some time at 114–115°C., and then oxidized with dry air or oxygen at 90–100°C., 2,2'-, 4,4'-, 3,3'-, and 2,3'-dipyridyls result (767a). The isomerization probably occurs at the tetrahydrodipyridyl (I) stage.

The formation of either 2,2'- or 4,4'-tetrahydrodipyridyl may be compared to the reduction of acetone by magnesium amalgam to tetramethylethylene glycol, or pinacol, in accordance with the equation:

$$
2(\text{CH}_3)_2\text{CO} + \text{Mg} \longrightarrow \begin{array}{c} (\text{CH}_3)_2\text{CO}^- \\ | \\ (\text{CH}_3)_2\text{CO}^- \end{array} \text{Mg}^{++} \xrightarrow{\text{H}_2\text{O}} \begin{array}{c} (\text{CH}_3)_2\text{COH} \\ | \\ (\text{CH}_3)_2\text{COH} \end{array} \tag{16}
$$
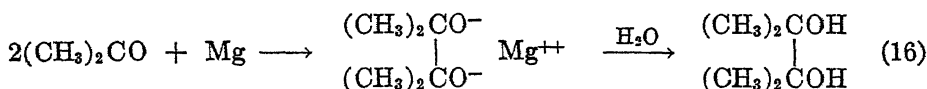
The reactions are of course not strictly analogous, because acetone is a ketone, while pyridine is an ammono aldehyde ether. Tetrahydro-2,2'-dipyridyl (III)

$$
\begin{array}{c}
\text{CH} \qquad\qquad \text{CH} \\
\diagup \quad \diagdown \qquad \diagup \quad \diagdown \\
\text{HC} \qquad \text{CH} \quad \text{HC} \qquad \text{CH} \\
\| \qquad\quad | \qquad\quad | \qquad\quad \| \\
\text{HC} \qquad \text{CH}\text{——}\text{CH} \qquad \text{CH} \\
\diagdown \quad \diagup \qquad\quad \diagdown \quad \diagup \\
\text{NH} \qquad\qquad \text{NH} \\
\text{III}
\end{array}
$$
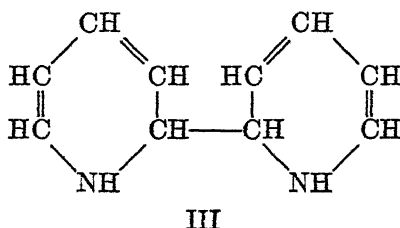
is an ammono glycol ether, because of the grouping

$$
\begin{array}{c}
\text{—CHNH—} \\
| \\
\text{—CHNH—}
\end{array}
$$
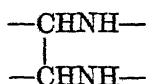
while tetrahydro-4,4'-dipyridyl (I, Na replaced by H) is its vinylogue; it is at the same time a 1,4-dihydropyridine derivative (see Section II, C, (g)).

4,4'-Dipyridyl is probably most readily prepared by reducing pyridine with zinc dust and acetic anhydride to the diacetyl derivative of tetrahydro-4,4'-dipyridyl (249), and oxidizing this, preferably with oxygen gas, to the dipyridyl. The preparation of 2,2'-dipyridyl is described in the next section.

E. OXIDATION OF PYRIDINE

Pyridine is stable or resistant toward neutral permanganate in the cold (375) or towards warm chromic acid (1, 10). Chemical oxidation under other conditions may lead to more or less complete rupture of the pyridine ring, with the formation of carbon dioxide and ammonia (235, 758, 822). Oxidation of pyridine—a cyclic ammono aldehyde ether—to the corresponding cyclic ammono aquo acid ester, 2-hydroxypyridine, is accomplished by dry potassium hydroxide at an elevated temperature (see Section II, G).

2,2'- and 4,4'-dipyridyls may be regarded as oxidation (or nitridation) products of pyridine in the sense that diacetyl, $CH_3COCOCH_3$, may be considered an oxidation product of acetaldehyde, CH_3CHO. Hein and Retter (417, 418), followed by Morgan and Burstall (627), oxidized pyridine with anhydrous ferric chloride at temperatures around 340°C., and obtained 2,2'-dipyridyl in fair yield, together with other dipyridyls and 2,2',2''-tripyridyl. 2,2'-Dipyridyl is also formed, though in less satisfactory yields (14–20 per cent), by heating pyridine for 4–5 hr. with an alumina–nickel catalyst at 320–325°C. (814).

Oxidation of pyridine homologues when properly carried out will give pyridinecarboxylic acids, though sometimes in poor yield because of destruction of the ring, which can be brought about by overheating with the oxidizing agent (758, 796, 822).

Perbenzoic acid oxidizes pyridine to pyridine N-oxide, $C_5H_5N{\rightarrow}O$ (591), while alkali persulfates may lead to complete oxidative degradation (261). Baumgarten and Dammann (39, 40) have, however, found that oxidation with aqueous potassium persulfate under milder conditions (heating for 2–3 hr.) gives as the chief product 2-pyridylpyridinium sulfate (II), which was isolated as the perchlorate. Autoöxidation of aqueous sulfite solutions for several hours in the presence of pyridine gives a mixture of 2- and 3-pyridylpyridinium salts (40, 41).

The formation of a 2-pyridylpyridinium salt is given below in equation 17. It will be noted that one pyridine ring can readily be opened, as with Zincke's dinitrophenylpyridinium chloride (see Section II, C, (a)), while the simultaneous formation of 2-aminopyridine (or of 3-aminopyridine in the case of the 3-pyridylpyridinium salts) is indicative of its structure. The resemblance to the reactions undergone by the analogous 4-pyridylpyridinium salts (see Section II, I, 5) is marked.

$$\xrightarrow{\text{2C}_6\text{H}_5\text{NH}_2\cdot\text{HCl}}$$

$$
\begin{array}{c}
\text{CH} \\
\diagup \quad \diagdown \\
\text{HC} \qquad \text{CH} \\
\parallel \qquad | \\
\text{C}_6\text{H}_5\text{NHCH} \qquad \text{CH}=\text{NC}_6\text{H}_5\text{Cl} \\
\text{IV}
\end{array}
$$

$$
+ \quad \text{NH}_2\text{C}
\begin{array}{c}
\text{N}-\text{CH} \\
\diagup \qquad \diagdown \\
\qquad \qquad \text{CH} \\
\diagdown \qquad \diagup \\
\text{CH}=\text{CH} \\
\text{V}
\end{array} \quad (17)
$$
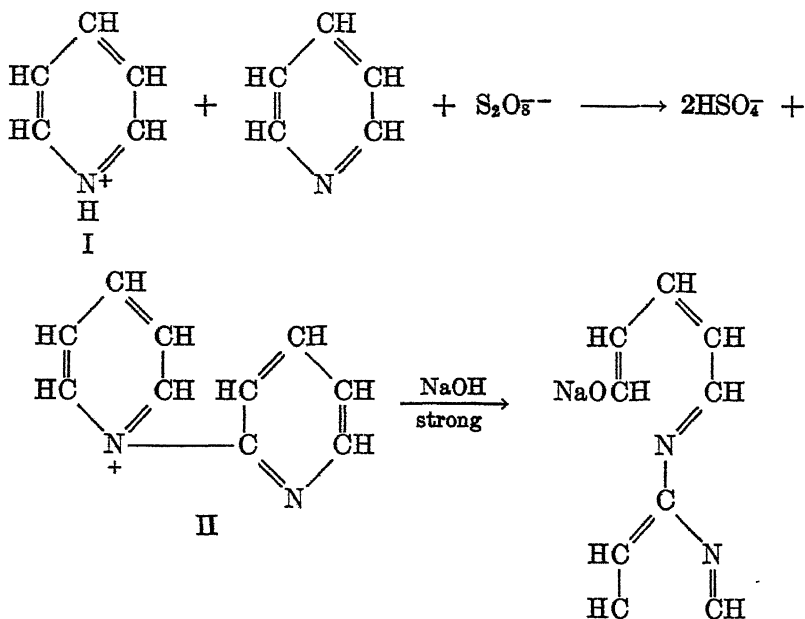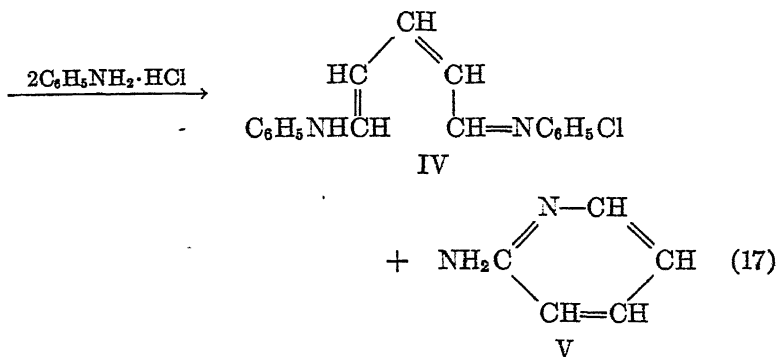
Baumgarten and Dammann (39) interpret the reaction as follows: The hydrogen attached to the nitrogen of the pyridinium ion (I) and an alpha hydrogen of a molecule of pyridine are removed by the persulfate; this is followed by a coupling of the two residues so formed. One can regard the 2-pyridylpyridinium salts (II) as quaternary ammonium salts formed by adding to a molecule of pyridine a second molecule of pyridine with an ionizable substituent in the 2-position:

$$
\begin{array}{c}
\text{CH}=\text{CH} \\
\diagup \qquad \diagdown \\
\text{HC} \qquad \qquad \text{N} \\
\diagdown \qquad \diagup \\
\text{CH}-\text{C} \\
| \\
\text{X}
\end{array}
$$
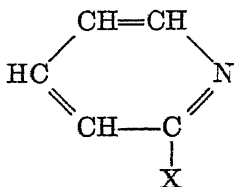
where X may be HSO_4, or a related group.

F. THE ACTION OF METALLOÖRGANIC COMPOUNDS ON PYRIDINE

The action of the Grignard reagent on pyridine in ether under ordinary conditions gives addition compounds of low solubility, such as $(2C_5H_5N + CH_3MgI + (C_2H_5)_2O)$ and $(2C_5H_5N + C_6H_5MgBr + (C_2H_5)_2O)$ (641a, 642, 643). It is probable that one pyridine molecule, at least, becomes attached to the heterocyclic nitrogen by a coördinate bond, as in the partial formula:

$$
\left[\overset{\diagdown}{\underset{\diagup +}{N}} \rightarrow \text{Mg}-\text{C}_6\text{H}_5 \right] \text{Br}^-
$$
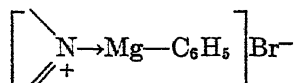
The nitrogen will therefore bear a positive charge, and it is possible that this may exert some activating effect on the reactions that are to be described, in the same manner that the ketonic reactivity of 2-methylpyridine is increased by the formation of a quaternary salt of the type of the methiodide (see Section II, I).

If an excess of Grignard reagent is heated with pyridine in diethyl ether at temperatures of 150–160°C. (62), alkyl- and aryl-pyridines are formed, though in rather variable yields. It is interesting to find 2,6-diphenylpyridine among the products of this high-temperature Grignard reaction (820); presumably it signifies that the addition compound (II below) loses MgBrH or its equivalent and gives free 2-phenylpyridine, which in turn reacts with phenylmagnesium

bromide to give diphenylpyridine. The related preparation of 2-phenylquino-
line from quinoline was carried out some years ago by Oddo (641). The reactions
probably follow the equation:

$$
\begin{array}{ccc}
\text{I} & \text{II} & \text{III}
\end{array}
\tag{18}
$$
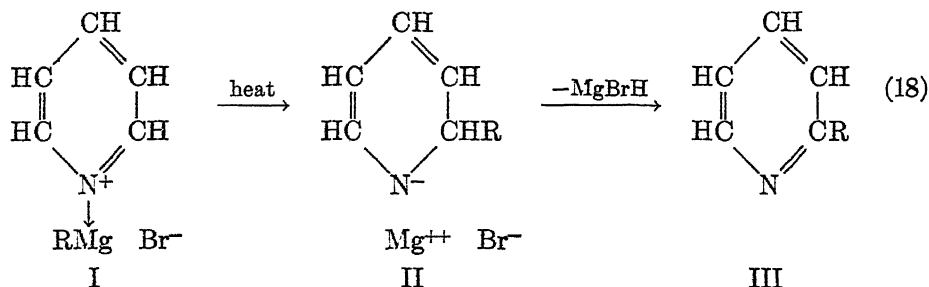
It is assumed, for the purposes of writing the equation, that the addition com-
pound (I) first formed between pyridine and the Grignard reagent contains only
one molecule of each. The loss of MgBrH or of MgBr₂ and MgH₂ from II is in
agreement with Ziegler's proposed mechanism for the reaction between pyridine
and the lithium alkyls and aryls (831a). Certainly, magnesium bromohydride
or magnesium hydride have never been isolated in these reactions, because they
doubtless reduce organic matter that is present.

Lithium alkyls and aryls react more smoothly and at a lower temperature with
pyridine than do the Grignard reagents. Ziegler and Zeiser (825) thus treated
2-butylpyridine with an excess of butyllithium at 100°C. and prepared 2,6-
dibutylpyridine. Evans and Allen (285; cf. 831b) heated the product of action
of phenyllithium on pyridine for 8 hr. in toluene and obtained 2-phenylpyridine
in 40–50 per cent yield. 2-Butylpyridine was similarly prepared from pyridine
and butyllithium in a nitrogen atmosphere at 90–100°C., together with lithium
hydride, which separated during the heating (831a). Although the latter was
not actually isolated, its presence was inferred from the almost theoretical
amount of hydrogen that was obtained on hydrolysis.

G. THE ACTION OF BASES ON PYRIDINE

Chichibabin (114, 121, 131) prepared the potassium salt of 2-hydroxypyridine
(2-pyridone) by heating pyridine with dry potassium hydroxide at 300–320°C.,
in the manner shown by the equation:

$$
+ \text{KOH} = + \text{H}_2
\tag{19}
$$
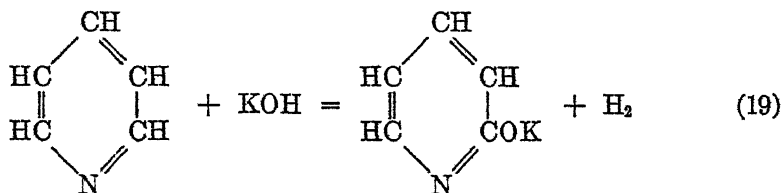
Potassium hydroxide has oxidized a cyclic ammono aldehyde ether to the po-
tassium salt of a cyclic ammono aquo acid ester, 2-hydroxypyridine. Previously,
Kudernatsch (547) melted 3-hydroxypyridine with sodium hydroxide and a little

water and obtained 2,5-dihydroxypyridine. The hydrogen evolution begins at about 290°C., and is over in about 35 min.

Chichibabin and Seide (158) in 1914 prepared 2-aminopyridine and 2,6-diaminopyridine (as sodium salts, I and II) by heating pyridine with sodium amide under xylene or other inert liquids. The reaction may be expressed as follows:

$$\text{(pyridine)} + \text{NaNH}_2 = \text{(2-aminopyridine sodium salt)} + \text{H}_2 \qquad (19a)$$

$$\text{I} + \text{NaNH}_2 = \text{(II)} + \text{H}_2$$

II
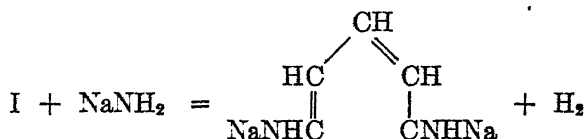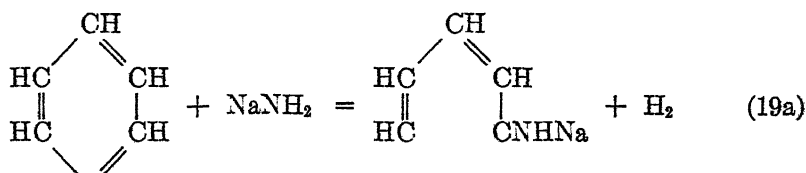
The preparation of the diaminopyridine requires a higher temperature and a larger amount of sodium amide than is necessary in making monoaminopyridine.

Generally this reaction and others of its type are carried out by heating pyridine and its homologues with sodium amide in boiling toluene, xylene, or in mineral oil at temperatures that may go as high as 160–180°C. Recently, Leffler (556), following a suggestion of Ostromislenski (649), has recommended the use of dimethylaniline as a reaction medium.

The introduction of an amino group into the 4-position of the pyridine ring proceeds with more difficulty than in the 2- or 6-position. The preparation of 2,4,6-triaminopyridine has been disclosed in a foreign patent (668). Further references to this important type of reaction must be omitted here, but they can be found in articles by Leffler (556) and by Fernelius and the author (61, 61a; cf. 116).

There seems to be a fairly general agreement that the reaction between sodium amide and pyridine is to be represented essentially by the following series of reactions:

$$\text{(pyridine)} \xrightarrow[\text{heat}]{\text{NaNH}_2} \text{(II)} \xrightarrow[\text{−NaH}]{\text{heat}} \text{(III)}$$

II   III

$$\xrightarrow[\text{or NaH}]{\text{NaNH}_2} \quad \begin{array}{c} \text{CH} \\ \text{HC} \diagup \diagdown \text{CH} \\ \text{HC} \diagdown \diagup \text{CNHNa} \\ \text{N} \end{array} \quad \xrightarrow{\text{H}_2\text{O}} \quad \begin{array}{c} \text{CH} \\ \text{HC} \diagup \diagdown \text{CH} \\ \text{HC} \diagdown \diagup \text{CNH}_2 \\ \text{N} \end{array} \quad (20)$$
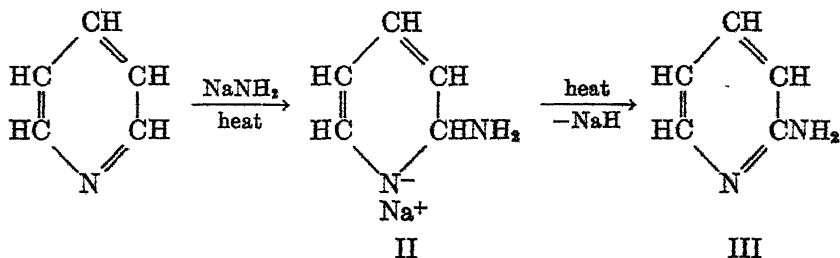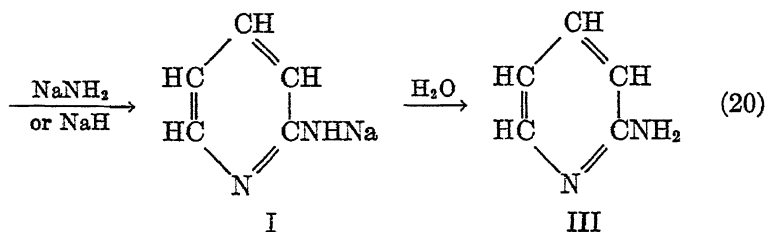
$$\qquad\qquad\qquad\qquad\qquad I \qquad\qquad\qquad\qquad III$$

The formation of II is reasonable, since sodium amide has been found to add to the related carbonyl group of some aquo ketones (391).

Objection might be raised to assuming that 2-aminopyridine (III) is itself an intermediate in this reaction, rather than its sodium salt (I); a mechanism has been given (see under quinoline, Section IV, H, 4; reference 56) which avoids this difficulty. The 2- and 6-positions of pyridine are equivalent because of resonance in the ring, while the reactivity of the 4-position will be somewhat less because of damping in transmission of the effect of the —C=N— grouping along a conjugated chain. From the standpoint of the ammonia system, pyridine, a cyclic ammono aldehyde ether, has been nitridized to 2-aminopyridine, a cyclic ammono acid ester.

2-Methylaminopyridine is formed (786) when pyridine and methylamine are heated with the eutectic of sodium amide and potassium amide (541) for several hours at 80°C.; similar reactions have been carried out with quinoline (see section IV, H, 4). Two interpretations of the reaction mechanism may be given: (1) The mixed alkali amides (=MNH₂) react with methylamine, possibly reversibly, to form an alkali methylamide, as expressed by the equation:

$$\text{CH}_3\text{NH}_2 + \text{NaNH}_2 \rightleftarrows \text{CH}_3\text{NHNa} + \text{NH}_3 \qquad (21)$$

It was, however, found experimentally that the higher amines ($\text{C}_4\text{H}_9\text{NH}_2$ and others) gave off very little ammonia when heated with sodium amide, owing either to the formation of a coating of insoluble alkali alkylamide on the mixed amides that prevented further reaction, or to the retention of ammonia by the alkali alkylamide as ammonia of "crystallization." The equation for the synthesis of methylaminopyridine would then be the following:

$$\text{C}_5\text{H}_5\text{N} + \text{CH}_3\text{NHM} = \text{C}_5\text{H}_4\text{NN(M)CH}_3 + \text{H}_2 \qquad (22)$$

When hydrolyzed,

$$\text{C}_5\text{H}_4\text{NN(M)CH}_3 + \text{H}_2\text{O} = \text{MOH} + \text{C}_5\text{H}_4\text{NNHCH}_3$$
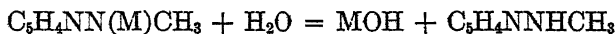
where M is sodium or potassium.

(2) It is perhaps a little more plausible at present to say that sodium amide (or potassium amide) adds normally to the pyridine to give an addition compound (II of equation 20 or 23), which reacts with methylamine in the manner below to form an intermediate (IV). This passes into methylaminopyridine or an alkali salt by loss of sodium hydride.

$$\text{II} \quad + \quad CH_3NH_2 \quad = \quad \text{IV} \quad + \quad NH_3 \tag{23}$$

$$\text{IV} \quad - \quad NaH \quad = \quad \text{(structure)}$$

$$-NHCH_3 + NaH \rightarrow H_2 + -N(Na)CH_3$$
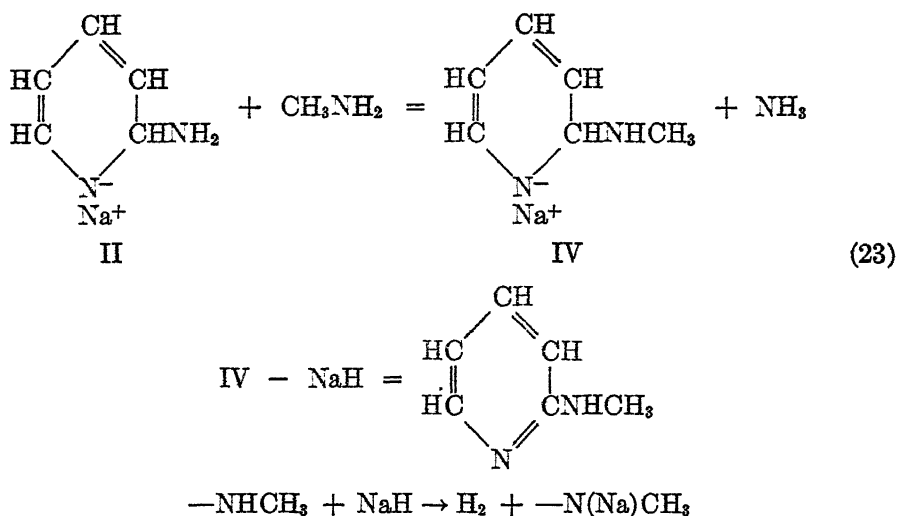
The conversion of II to IV may be reversible. Compound II is a salt of an ammono meroacetal,

$$RCH \begin{array}{c} NH_2 \\ \\ N(Na)R' \end{array}$$
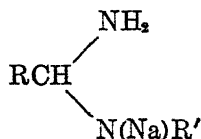
and is therefore sufficiently reactive to undergo the above changes with ease. It will be shown subsequently that many similar reactions are known, particularly among the ammono aquo meroacetals, such as the pyridine and quinoline pseudo bases and cotarnine (see Sections II, I, 7; IV, N, 2; V, I).

H. ALKYLATED AND ARYLATED PYRIDINES

2-Methylpyridine (α-picoline, I) and 4-methylpyridine (γ-picoline, II) are cyclic ketone ethers of the ammonia system; furthermore, in view of the previous discussion of vinylogy (Section I, I) it will be seen that the 4- and 6-hydrogens of I and the 2- and 6-hydrogens of II will behave much as do the 2-, 4-, or 6-hydrogens of unsubstituted pyridine. 2,4-Dimethylpyridine (III), 2,6-dimethylpyridine (IV), and 2,4,6-trimethylpyridine (sym-collidine, V) all should show ketonic reactivity similar to that of the α- and γ-picolines.

I   II

$$
\begin{array}{ccc}
\text{III} & \text{IV} & \text{V}
\end{array}
$$
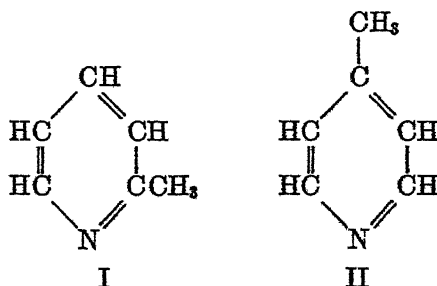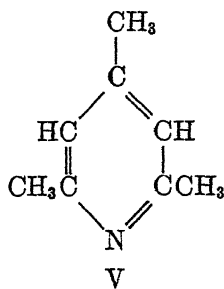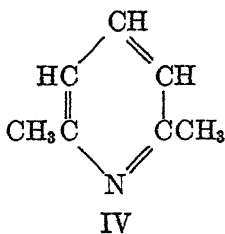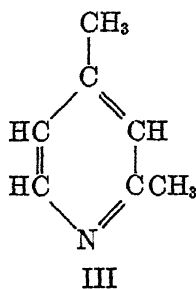
Among the large number of reactions of these compounds are the following:

(*1*) Like the aquo methyl ketones of the type of acetone or acetophenone, 2- and 4-methylpyridines form alkali-metal salts when they are treated with sufficiently strong bases, as shown by equations 24 and 25 (54, 117, 669, 827):

$$+ \; \text{LiC}_6\text{H}_5 \xrightarrow{\ \text{ether}\ }$$

$$\text{C}_6\text{H}_6 \; + \quad \rightleftarrows \qquad\qquad (24)$$

$$+ \; \text{NaNH}_2 \; (\text{or KNH}_2) \; = \; \text{NH}_3 \; +$$

$$\rightleftarrows \qquad\qquad (25)$$
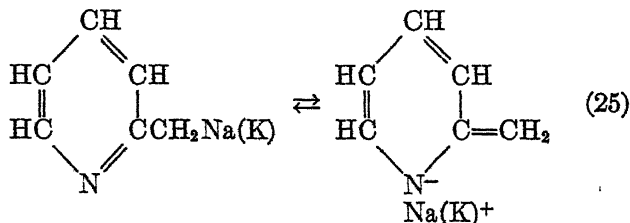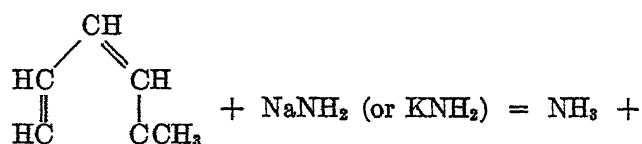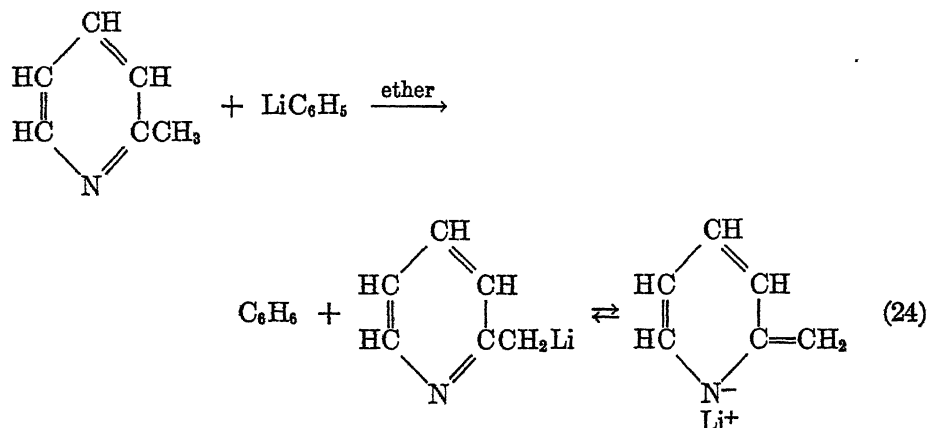
Presumably the alkali-metal salts of the picolines are tautomeric in the sense that the sodium salt of acetoacetic ester is. The tautomerism of the parent compound, 2-picoline, was discussed some time ago by Chichibabin (115; *cf.* Mills and Smith (625)).

A number of examples of the type of syntheses that can be carried out with these highly reactive salts follow.

(a) $C_5H_4NCH_2Na + RX = C_5H_4NCH_2R$ (or $C_5H_4NCHR_2$) $+ NaX$
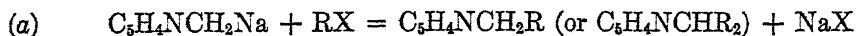
where RX is an alkyl halide. The method of Chichibabin for carrying out this reaction is the following (117a):

The pyridine base, with a methyl group in the 2-, 4-, or 6-position, is mixed, without other solvent, with an excess (calculated on the basis of alkyl halide) of finely pulverized sodium amide of good quality; the liquid becomes yellow, yellow brown, or brown violet. The appropriate alkyl halide is slowly added with cooling, and the reaction products fractionally distilled, after hydrolysis destroys the sodium salts. The yields are usually from 50 to 60 per cent of the mono-substitution product and up to about 20 per cent of the disubstitution product. The ease of formation of metallic derivatives decreases in the order 4-picoline (4-methyl-3-ethylpyridine, 2-picoline), 2,6-dimethylpyridine.

2- and 4-Picolines have similarly been converted to phenylethylpyridines and phenylpropylpyridines through the potassium salt in liquid ammonia (65b). 12-(2-Pyridyl)-1-decene (or -2-decene) has been made from undecylene chloride, 2-picoline, and sodium amide (87a), following Chichibabin's method as modified by Knight and Shaw (474a), who operated at a temperature of 100°C. Ziegler and Zeiser (830) report the preparation of 2-(β-phenylethyl)pyridine from the lithium salt of 2-picoline (cf. 48a).

(b) Sodium 2-picolyl reacts with benzophenone to form an addition product which, after hydrolysis, gives diphenyl-α-picolylcarbinol.

$C_5H_4N—CH_2Na + (C_6H_5)_2C{=}O$

$$(C_6H_5)_2C\diagup{}^{ONa}_{\diagdown CH_2—C_5H_4N(2)} \xrightarrow{H_2O} (C_6H_5)_2C\diagup{}^{OH}_{\diagdown CH_2—C_5H_4N(2)} \qquad (26)$$
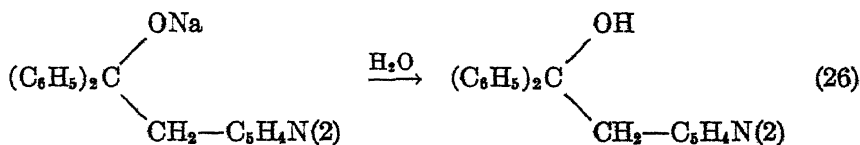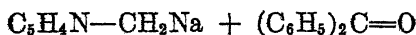
Here, sodium picolyl behaves like a Grignard reagent (133).

In a similar fashion, lithium 2-picolyl reacts with benzaldehyde to form phenyl-(pyridylmethyl)carbinol, $C_6H_5CHOHCH_2C_5H_4N$ (48, 133), and with acetalde-hyde to give methyl(2-picolyl)carbinol (805). 2-Phenacylpyridine is the product of condensation of benzoyl chloride with lithium 2-picolyl (48). Lithium picolyl reacts with acetic anhydride or with ethyl acetate to form, among other compounds, 2-acetonylpyridine (43; this is called "dehydroisopelletierine" in the abstracts).

(c) Chichibabin (117b) treated α- and γ-picolines with sodium amide and β-chloroethyl ethyl ether, $ClCH_2CH_2OC_2H_5$, and obtained pyridylpropyl ethyl ethers of the general formula $C_5H_4NCH_2CH_2CH_2OC_2H_5$. Similarly, it was

found that γ-picoline, chloroacetal, and sodium amide react to form 1,1-diethoxy-3-(4'-pyridyl)propane, $C_5H_4NCH_2CH_2CH(OC_2H_5)_2$. Wibaut and Beets (813) were unable to prepare the corresponding derivative of α-picoline by Chichibabin's method, but were successful in carrying out the reaction between the lithium salt of α-picoline and bromoacetal in ether.

(d) Dirstine (250) and Seibert (752b) have catalytically phenylated the potassium salts of 2- and 4-methylpyridines in liquid ammonia, and have obtained yields of benzylpyridine, benzohydrylpyridine, and triphenylmethylpyridine that total as high as 80 per cent of the theoretical. Potassium amide, dissolved in liquid ammonia, was added to a solution of potassium picolyl and chlorobenzene in the same solvent. The peculiar activation of the aromatically bound halogen has not yet been satisfactorily explained, but is thought possibly to be due to the formation of o- or p-potassium salts of the type, $K^+ (C_6H_4Cl)^-$, from which halogen is more readily removed as an ion.

(2) The methyl group in 2- and 4-methylpyridines (but not in 3-methylpyridine; see reference 493) reacts with many aldehydes to undergo an aldol condensation, or an aldol condensation followed by loss of water (Claisen reaction). As expected, the corresponding reactions of open-chain aquo methyl ketones, such as acetone or acetophenone, are much more rapid. A few examples are listed below:

(a) 2-Picoline reacts with benzaldehyde and other aromatic aldehydes to form styryl or substituted styryl derivatives in the manner of the following equation:

α-Stilbazole
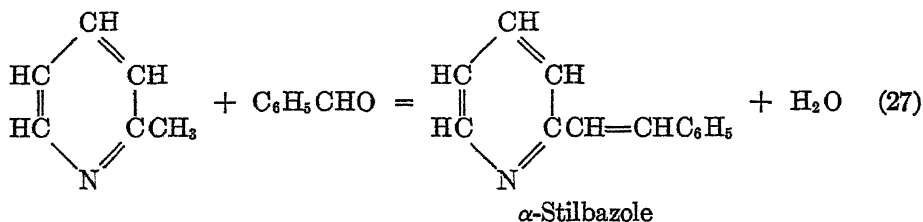
The corresponding reaction with 4-picoline is not as rapid. It is often necessary to heat in the neighborhood of 200°C. to bring about these condensations, even in the presence of an added catalyst, such as zinc chloride.

Shaw and Wagstaff (759; cf. 44) claim that better yields of α-stilbazoles (see equation 27) are formed by refluxing 2-methylated pyridines with aromatic aldehydes in the presence of acetic anhydride, and without the addition of zinc chloride. Parallel reactions without a condensing agent (zinc chloride or acetic anhydride) gave mixtures of alkines (I) and stilbazoles (II), the former being produced by an aldol-like condensation, and passing by loss of water into the latter, as shown by equation 28:

$$C_5H_4NCH_3 + RCHO = C_5H_4NCH_2CH(OH)R =$$
$$I$$

$$C_5H_4NCH=CHR + H_2O \quad (28)$$
$$II$$
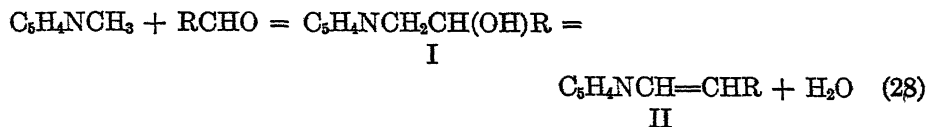
The alkines are converted to stilbazoles by boiling for an hour with acetic anhydride, and to the aldehyde and 2-picoline (to some extent) by heating with water (140°C.; 10 hr.). The formation of alkines is therefore reversible, just as is the

ordinary aldol condensation. The function of the condensing agent seems therefore to convert intermediates of the general formula I to stilbazoles, as well as to increase the velocity of the over-all reaction. However, Roth (731) reports his inability to dehydrate with zinc chloride the alkine formed by condensing o-nitrobenzaldehyde and 2-picoline.

The preparation of the pure alkines (I) from 2-methylpyridine and aromatic aldehydes is accomplished by heating the two in the presence of a little water at temperatures in the neighborhood of 140–160°C. (21a, 566, 731) for 10 hr. or more.

Feist, Awe, and Kuklinski (288a) find that substituted styryl derivatives are not formed by heating benzaldehydes with 2-amino-6-methylpyridine, 2-dimethyl-amino-6-methylpyridine, 2-methylamino-6-methylpyridine, or 2-acetamido-6-methylpyridine. 2-Amino-6-methylpyridine condenses with these aldehydes to give Schiff bases instead.

2-Picoline (and 4-picoline as well) reacts with aqueous formaldehyde at temperatures of about 130–150°C. and over a period of 10–15 hr. to form monomethylolpicoline, dimethylolpicoline, and trimethylolpicoline (501a, 565d, 567, 567a, 590; cf. 798). The formation of the latter two is of course favored by an excess of formaldehyde. The reactions follow the equations below:

$$C_5H_4NCH_3 \xrightarrow{HCHO} C_5H_4NCH_2CH_2OH \xrightarrow{HCHO}$$

$$C_5H_4NCH(CH_2OH)_2 \xrightarrow{HCHO} C_5H_4NC(CH_2OH)_3 \quad (29)$$
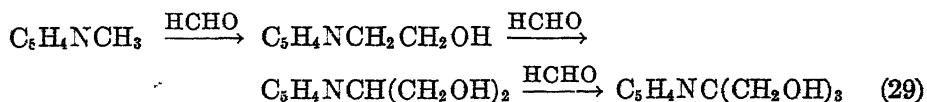
Methyl(2-pyridyl)carbinol and ethyl(2-pyridyl)carbinol are similarly obtained from 2-picoline and aqueous acetaldehyde or propionaldehyde, respectively, though in comparatively poor yields (550, 552; see also 805 and 797).

Chloral and 2-(or 4-)picoline react when heated to form picolyltrichloromethylcarbinols, $C_5H_4NCH_2CH(OH)CCl_3$ (276, 798).

McElvain and Johnson (568) have heated 2-picoline and quinaldine with active carbonyl compounds at 140°C., and have obtained condensations in the sense of equation 30:
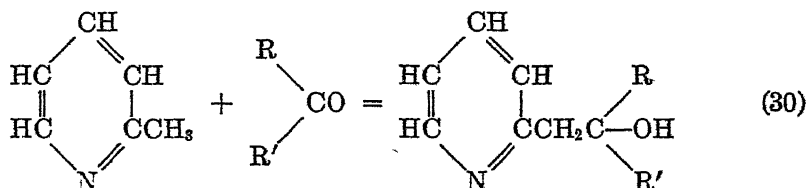
Some of their results are listed below:

TIME AT 140°C.	R	R′	YIELD OF PURE PRODUCT
hours			*per cent*
2.0	COOC$_2$H$_5$	COOC$_2$H$_5$	33
1.5	C$_6$H$_5$CO	C$_6$H$_5$CO	16
1.0	C$_6$H$_5$CO	COOC$_2$H$_5$	74
4.0	C$_6$H$_5$	C$_6$H$_5$CO	54

Condensations of polymethylated pyridines

2,6-Dimethylpyridine reacts with benzaldehyde in the presence of zinc chloride at elevated temperatures to form a distyryl derivative (751), indicating that both methyl groups are equally reactive, as might be expected because of the ring resonance.

Clemo and Gourlay (170) heated 2,4-dimethylpyridine (α,γ-lutidine) with benzaldehyde and acetic anhydride (reflux for 16 hr.) and obtained 2-styryl-4-methylpyridine and 2,4-distyrylpyridine in the approximate ratio of two to one. Bachér (22), who previously carried out this reaction in the presence of zinc chloride (7 hr. at 225°C.), reported only 2-styryl-4-methylpyridine. Similarly, Langer (554) found that p-tolualdehyde condenses with 2,4-dimethylpyridine in the 2-position, forming both the styryl derivative and its corresponding alkine, the latter in smaller quantity.

It is therefore apparent that a methyl group in the 2-position of the pyridine nucleus is more reactive than when it is in the 4-position, pointing to the fact that there is some damping in the transmission of the effect of the —C=N— to the methyl along the conjugated chain (for discussion of damping, see reference 87).

(3) The 2- and 4-picolines react with heated sodium amide under an inert hydrocarbon oil to give, respectively, 6-amino-2-methylpyridine and 2-amino-4-methylpyridine (158, 753, 754), therefore behaving as unsubstituted pyridine would under the same conditions. 2,6-Dimethylpyridine is harder to convert to an amino derivative (NH_2 in position 4) than are the 2- and 4-picolines (128), perhaps largely because of the lower reactivity of the 4-hydrogen. If sodium amide and the dimethylpyridine react under the conditions of the experiment to form a sodium salt, the negative charge on the side-chain carbon should hinder a reaction which depends upon the attack of the pyridine nucleus by an active anion, NH_2^-.

(4) 2-Picoline reacts with selenium dioxide, when heated, to give the corresponding pyridinecarboxylic acid, together with a small amount of pyridine-2-aldehyde (81, 420, 422). The use of selenium dioxide to convert a methyl attached to carbonyl to an aldehyde group is well known (704). A typical example is the preparation of phenylglyoxal in accordance with the following equation:

$$C_6H_5COCH_3 + SeO_2 = C_6H_5COCHO + Se + H_2O \qquad (31)$$

I. QUATERNARY PYRIDINIUM SALTS

Pyridine and many other substances containing tertiary nitrogen react with alkyl iodides, alkyl sulfates, and alkyl p-toluenesulfonates to form quaternary ammonium salts in the manner of the representative equation below:

$$C_5H_5N + CH_3I = [C_5H_5\overset{+}{N}CH_3]I^- \text{ or } [C_5H_5NCH_3]^+I^- \qquad (32)$$
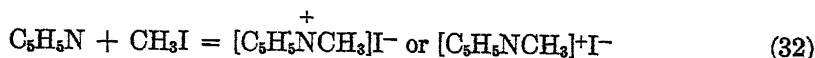
In the quaternary ammonium salt above, the nitrogen of the pyridine bears a positive charge; supposedly this charge is distributed by resonance, in small measure at least, to the 2- and 4-carbon atoms. The formula on the right of equation 32 is therefore to be preferred.

The charged nitrogen atom has not affected the essential character of the double bond between carbon and nitrogen. For this reason, pyridine methiodide —or rather the N-methylpyridinium ion—is still a cyclic ammono aldehyde ether, and 2-methylpyridine is a cyclic ammono ketone ether, although of somewhat more active types than hitherto encountered in this review. The distributed positive charge on the cation will markedly accelerate reactions involving active anions (i.e., bases) either directly or as catalysts. The close resemblance of pyridinium and pyrylium salts has previously been commented upon, and will be elaborated in detail later (Section III).

There follows a list of some characteristic reactions of the quaternary pyridinium salts:

1. Formation of styryl derivatives

2-Methylpyridine methiodide and p-dimethylaminobenzaldehyde are refluxed in alcoholic solution for 5 hr., with the addition of a small amount of piperidine as a catalyst. There is obtained 2-p-dimethylaminostyrylpyridine methiodide, a sensitizer of photographic plates for green light (616).
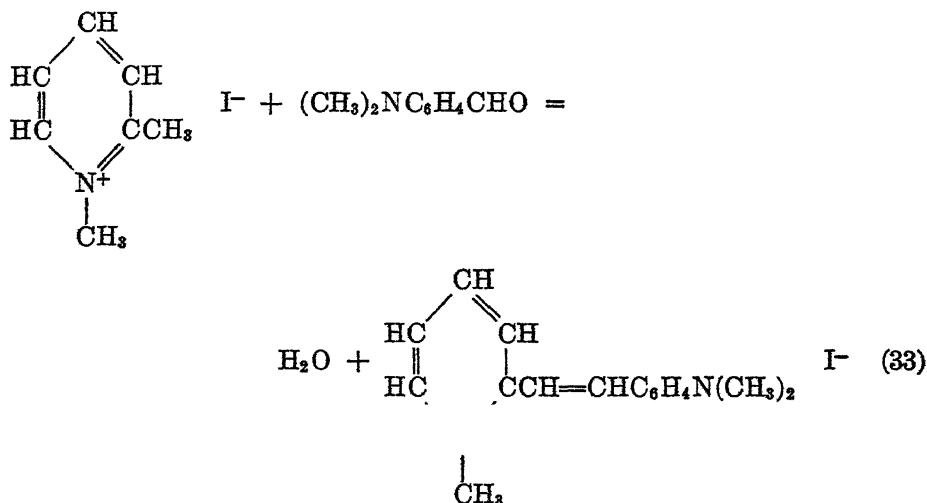
Picoline methiodide thus condenses more rapidly with aldehydes and in the presence of a more mildly acting catalyst than does picoline itself, showing clearly the accelerating effect of quaternary salt formation on reactivity. Many other condensations of this type have been described recently (171, 172, 183, 259, 260, 604).

2. Reaction with nitrosodimethylaniline

p-Nitrosodimethylaniline (I) resembles the ketones to some extent in its reactivity, but it fails to condense with 2-picoline under any conditions that have been tried. Nevertheless, it reacts without difficulty with 2-picoline methiodide or ethiodide in the presence of piperidine to form an alkiodide of the p-dimethylamino anil of pyridine-2-aldehyde (II) (462).

$$
\begin{array}{c}
\text{CH} \\
\text{HC} \diagup \diagdown \text{CH} \\
\text{HC} \diagdown \diagup \text{CCH}_3 \\
\text{N}^+ \\
\text{CH}_3 \\
\text{(cation only)} \quad \text{I}
\end{array}
\;+\; (CH_3)_2NC_6H_4NO \;=\;
\begin{array}{c}
\text{CH} \\
\text{HC} \diagup \diagdown \text{CH} \\
\text{HC} \diagdown \diagup \text{CCH}=NC_6H_4N(CH_3)_2 \\
\text{N}^+ \\
\text{CH}_3 \\
\text{II}
\end{array}
$$

$$+ \; H_2O \quad (34)$$
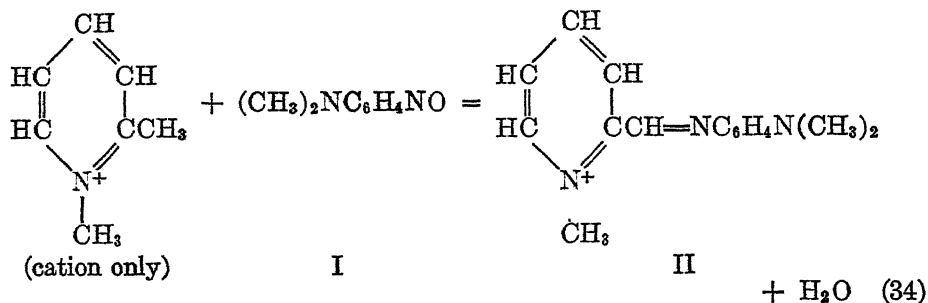
When II is heated with phenylhydrazine the dimethylaminophenyl group is replaced by —NHC$_6$H$_5$ to give

$$
\overset{+}{C_5H_4N}CH=NNHC_6H_5
$$
$$
\mid
$$
$$
CH_3
$$
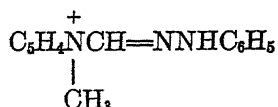
which splits off methyl iodide in a high vacuum to give the phenylhydrazone of pyridine-2-aldehyde. This can be hydrolyzed by heating with dilute hydrochloric acid to pyridine-2-aldehyde.

3. Cyanine dyes

Cyanine dyes may be prepared from the alkiodides of 2- and 4-methylpyridines by reactions that are dependent upon the activity of the methyl group. A brief discussion of this important class of compounds is given in Section IV, N, 9. A partial list of references to the preparation of cyanine dyes containing the pyridine nucleus is appended (88, 92, 93, 94, 259, 260, 402, 645, 719, 773).

4. 2-Halogenopyridine alkiodides

In a later section (II, M) it will be shown that 2-chloropyridine is a cyclic ammono acid chloride ester, and therefore contains a reactive chlorine atom. The activity of a halogen in the 2-position is enhanced by quaternary salt formation. Fischer (297) has thus prepared 2-anilinopyridine iodomethylate by heating 2-iodopyridine iodomethylate with aniline in alcoholic solution at 100°C., at the same time remarking that the 2-iodine atom in the quaternary salt is exchanged much more easily for the phenylamino group than is the chlorine in 2-chloropyridine. Pseudocyanines and cyanines may readily be prepared from the 2- or 4-iodopyridine alkiodides (92, 93, 94, 402; see Section II, I, 3).

Wibaut, Speekman, and Wagtendonk (814i) have prepared the methosulfate of 2,6-dibromopyridine, and find that it is converted by sodium hydroxide at room temperatures to 1-methyl-6-bromo-2-pyridone,

$$
\begin{array}{c}
\text{CH} \\
\text{HC} \diagup \diagdown \text{CH} \\
\text{BrC} \diagdown \diagup \text{C}=O \\
\text{N} \\
\text{CH}_3
\end{array}
$$
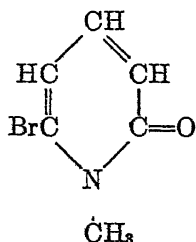
5. *Pyridylpyridinium salts*

The formation of 2- and 3-pyridylpyridinium salts by the oxidation of pyridine with persulfate or with atmospheric oxygen has been described previously (Section II, E). Rodewald and Plazek (715d, 715e) prepared 2-pyridylpyridinium iodide (I) by heating pyridine hydrochloride with iodine or iodine chloride for about 5 hr. at 280°C. The primary reaction product, 2-iodopyridine, adds to unchanged pyridine to give the quaternary salt (I).

$$
\begin{array}{c}
\text{CH} \\
\text{HC} \quad \text{CH} \qquad \text{CH=CH} \\
\text{HC} \quad \text{C—N} \qquad \quad \text{CH} \\
\text{N} \qquad \text{I}^- \quad \text{CH—CH}
\end{array}
$$
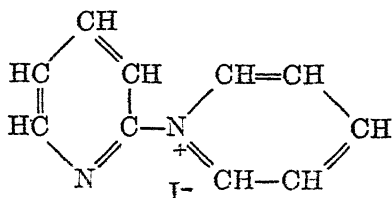
Iodinated pyridines are also formed in the reaction (see Section II, M, 1). 2-Aminopyridine may be made by the action of ammonia on the 2-pyridylpyridinium iodide, much in the manner of equation 17. (See reference 814f, pp. 709 and 717, for the corresponding chlorine compound.)

4-Pyridylpyridinium salts are among the products of the self-condensation of 4-chloro- and 4-bromopyridine (Section II, M, 2). Koenigs and Greiner (497a and b) prepared the best-known representative of this class of compounds, the hydrochloride of 4-pyridylpyridinium chloride (II of equation 35) by allowing dry pyridine (100 g.) and thionyl chloride (300 g.) to stand for 3 days at ordinary temperatures or by heating for 5 hr. on the water bath. The reaction is expressed by the equation below:

$$
\begin{array}{c}
\text{CH} \\
\text{HC} \quad \text{CH} \\
\text{HC} \quad \text{CH} \\
\text{N}
\end{array}
+ \text{SOCl}_2 = \text{addition compound}
$$

which rearranges to

$$
\begin{array}{c}
\text{Cl} \quad \text{H} \\
\text{C} \\
\text{HC} \quad \text{CH} \\
\text{HC} \quad \text{CH}
\end{array}
\tag{35}
$$

$$
\text{SOCl}
$$
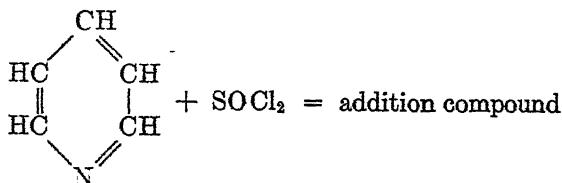
or perhaps to 4-chloropyridine itself; this reacts with unchanged pyridine to form the quaternary salt, 4-pyridylpyridinium dichloride (II).

II
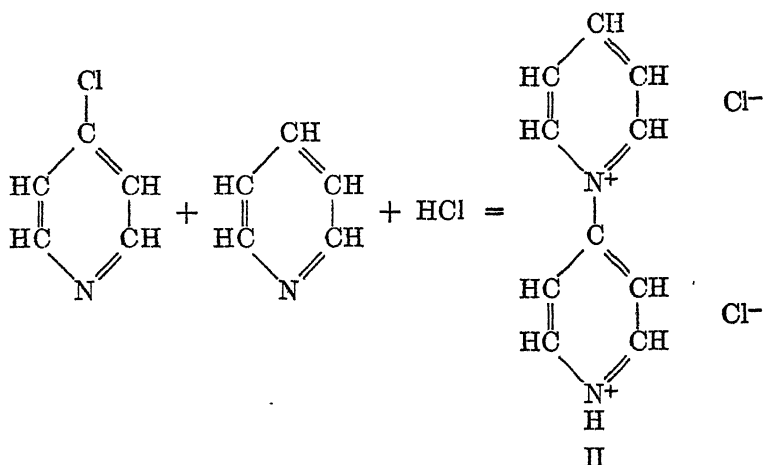
The above mechanism of Koenigs is probable in view of the fact that picolinic acid chloride (pyridine-2-carboxylic acid chloride) reacts with thionyl chloride to form 4-chloropicolinic acid chloride (601a). The exact fate of the thionyl chloride is unknown.

4-Pyridylpyridinium dichloride may be converted to a number of 4-substituted pyridines that are not otherwise readily available; at the same time, one of the pyridine rings is opened to form glutacondialdehyde, or a derivative. One typical reaction is the following:
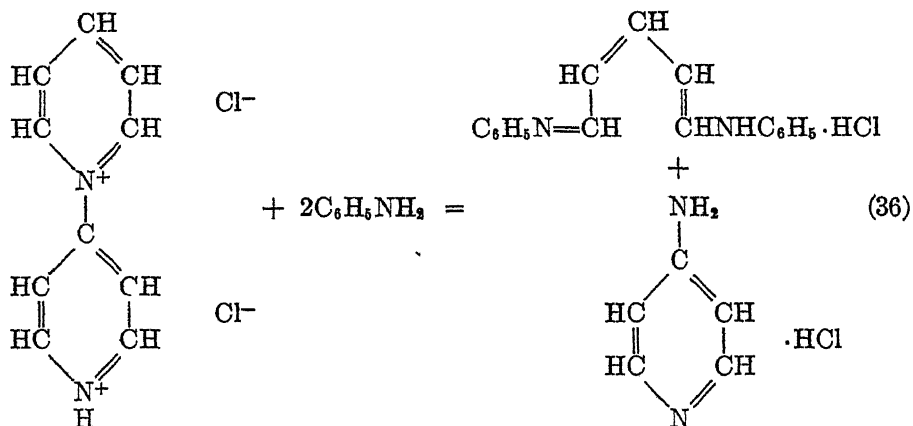
The action of aniline on 4-pyridylpyridinium dichloride has given 4-aminopyridine hydrochloride and the hydrochloride of the anil anilide of glutacondialdehyde.

4-Aminopyridine is, however, better made by heating 4-pyridylpyridinium dichloride with concentrated ammonia for 8 hr. in an autoclave at 150°C. 4-Hydroxypyridine is obtained by heating the quaternary salt with water for 8 hr. at 150°C. (70 g. from 200 g. of starting material).

The similarity between the reactions of 4-pyridylpyridinium dichloride and of

2,4-dinitrophenylpyridinium chloride (see Section II, C,1) is rather close. In both cases, a pyridine ring is opened to form glutacondialdehyde or a derivative. Accompanying this are the aminated compounds, 4-aminopyridine and 2,4-dinitroaniline, respectively.

The effect of the 2,4-dinitrophenyl group is promoting scission of the pyridine ring of 2,4-dinitrophenylpyridinium chloride was ascribed (Section II, C, 1) to the electron attraction of the two nitro groups ($-I$ $-T$ effects). The strong $-I$ effect of the positively charged nitrogen of the lower ring of pyridylpyridinium dichloride (equation 36) is of course not as great as the combined $-I$ $-T$ effects of the two nitro groups of dinitrophenylpyridinium chloride; therefore it is more difficult to open a pyridine ring in the former case.

6. Methylene bases (ammono enol ethers) or pyridone methides

Decker (192) treated 2-benzylpyridine methiodide (cation=I) with strong sodium hydroxide solution and obtained the orange-colored 2-benzylidene-1-methyl-1,2-dihydropyridine (II), in accordance with the equation:

$$
\begin{array}{cc}
\text{I} & \text{II}
\end{array}
\qquad (37)
$$
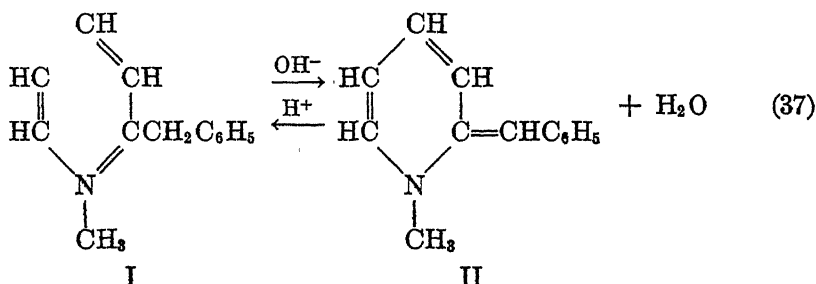
The mechanism of this change is not definitely known. If the hydroxyl ion adds to the 2-carbon atom, a pseudo base will result and II will be formed by removal of the elements of water. The suggestion has also been made that a hydrogen of the side-chain methylene ionizes to a slight extent under the influence of the electron attraction ($-I$ effect) of the positively charged nitrogen. Combination of the hydrogen ion so produced with the hydroxyl of the base will give III, a polar or "zwitter ion" form of the methylene base (II), with which it is doubtless in resonance.

$$
\begin{array}{cc}
\text{III} & \text{II}
\end{array}
$$
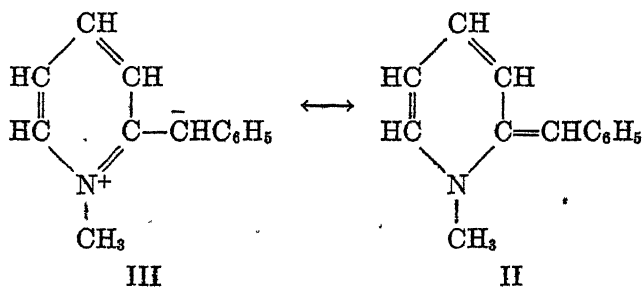
Benzene extracts the methylene base, II or III, from the product of the action of a base on the quaternary salt (I), while water in turn extracts the strong base,

1-methyl-2-benzylpyridinium hydroxide, from the benzene solution. This indicates an equilibrium between the two forms dependent not only upon hydrogen-ion concentration, but also upon the solvent (193a, 224a). Every methylene base examined by Decker (193a, 224a) behaves in a similar manner.

The related enamine, 1-methyl-2-methylene-1,2-dihydropyridine (formula II, $=CHC_6H_5$ replaced by $=CH_2$) is similarly prepared from 2-picoline methiodide and strong sodium hydroxide (748; cf. 633, 634). It is rather unstable, but it may be isolated in the form of addition compounds with phenyl isocyanate or carbon disulfide (635, 746a).

According to Mumm (635), the reaction with carbon bisulfide follows the equation:

$$
\begin{array}{ccc}
\text{III} & & \text{IV}
\end{array}
$$

$$
\underset{\text{III}}{
\begin{array}{c}
\text{CH} \\
\text{HC}\diagup\ \diagdown\text{CH} \\
\text{HC}\quad\quad\text{C}=\text{CH}_2 \\
\diagdown\text{N}\diagup \\
\text{CH}_3
\end{array}}
\;+\;
C\genfrac{}{}{0pt}{}{=S}{=S}
\;=\;
\underset{\text{IV}}{
\begin{array}{c}
\text{CH} \\
\text{HC}\diagup\ \diagdown\text{CH}\qquad\text{SH} \\
\text{HC}\quad\quad\text{C}=\text{CHC}\diagup \\
\diagdown\text{N}\diagup\qquad\qquad \diagdown\text{S} \\
\text{CH}_3
\end{array}}
\tag{38}
$$
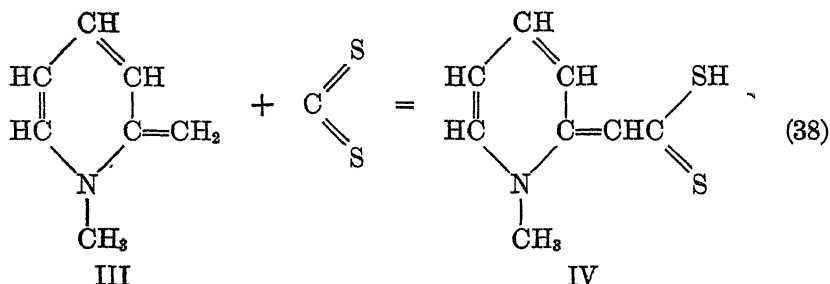
Evidence for formula IV is afforded by the conversion of its 3-carboethoxy derivative (V) into a cylic compound (VI), in accordance with the equation:

$$
\underset{\text{V}}{
\begin{array}{c}
\text{CH} \\
\text{HC}\diagup\ \diagdown\text{CCOOC}_2\text{H}_5 \\
\text{HC}\quad\quad\text{C}=\text{CHCSH} \\
\diagdown\text{N}\diagup\qquad\quad \text{S} \\
\text{CH}_3
\end{array}}
\;=\;C_2H_5OH\;+\;
\underset{\text{VI}}{
\begin{array}{c}
\text{CH}\quad\text{CO} \\
\text{HC}\diagup\ \diagdown\text{C}\diagup\ \diagdown\text{S} \\
\text{HC}\quad\quad\text{C}\quad\quad\text{C}=\text{S} \\
\diagdown\text{N}\diagup\ \diagdown\text{CH} \\
\text{CH}_3
\end{array}}
\tag{39}
$$
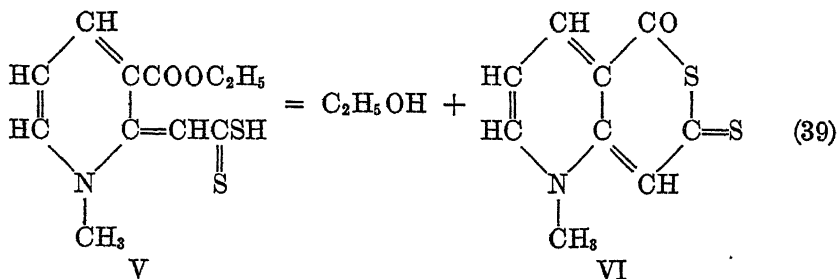
Earlier formulas (746; cf. 720) are regarded as improbable.

The phenyl isocyanate addition compound has formula VII (635, 747).

$$
\underset{\text{VII}}{
\begin{array}{c}
\text{CH} \\
\text{HC}\diagup\ \diagdown\text{CH} \\
\text{HC}\quad\quad\text{C}=\text{CHCONHC}_6\text{H}_5 \\
\diagdown\text{N}\diagup \\
\text{CH}_3
\end{array}}
$$
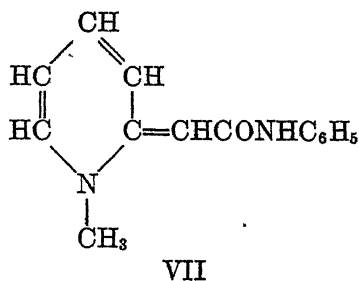
Many related methylene bases (= pyridone methides) have been prepared; a number of them are derived from 4-picoline (135, 143, 499, 633, 634, 748).

It has been known for a long time from the work of Chichibabin (115, 117a)
.hat 2- and 4-picolines (VIII, IX) are tautomeric with the enamic, or ammono
:nolic, forms (X, XI) shown below:

$$
\begin{array}{cccc}
\text{VIII} & \text{X} & \text{IX} & \text{XI}
\end{array}
$$

[structures VIII, X, IX, XI]
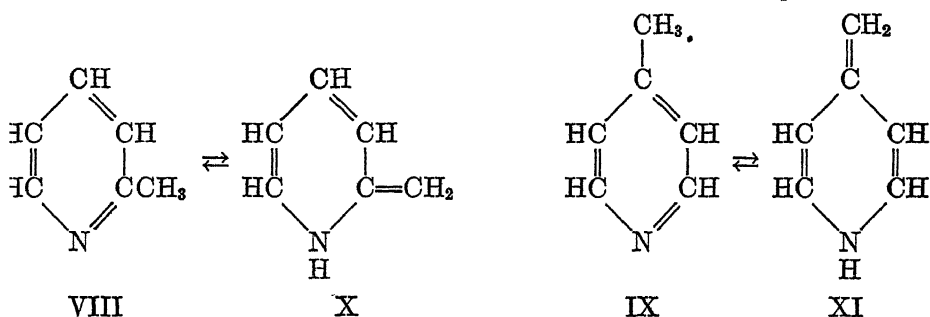
Phe methylene bases, or pyridone methides, are the *N*-ethers of X and XI and
ire therefore to be compared with the ethers of the aquo enols (e.g., with
$CH_2=CHOC_2H_5$) that were discussed briefly in Section II, C, (a). The occur-
·ence of methylene bases as intermediates in the condensations of the picoline and
quinaldine alkiodides which lead to the formation of cyanine dyes will be dealt
vith in section IV, N, 5, (a).

7. *Pseudo bases, carbinol bases, or 1-alkyl-2-hydroxy-1,2-dihydropyridines*

Pyridine halogen alkylates or pyridine methosulfates (I below) when treated
vith silver oxide and water, or with aqueous alkali, give first the strongly basic
V-alkylpyridinium hydroxides (II), which undergo partial isomerization to the
-alkyl-2-hydroxy-1,2-dihydropyridines (III), as expressed by equation 40
267, 409, 427; *cf.* 28):

$$
\text{I} \quad I^- + \quad \begin{array}{c} \text{NaOH} \\ \text{(or} \\ Ag_2O, H_2O) \end{array} \quad \rightleftarrows \quad \text{II} \quad OH^- + NaI \quad (40)
$$

[structures I and II]

III

[structure III]
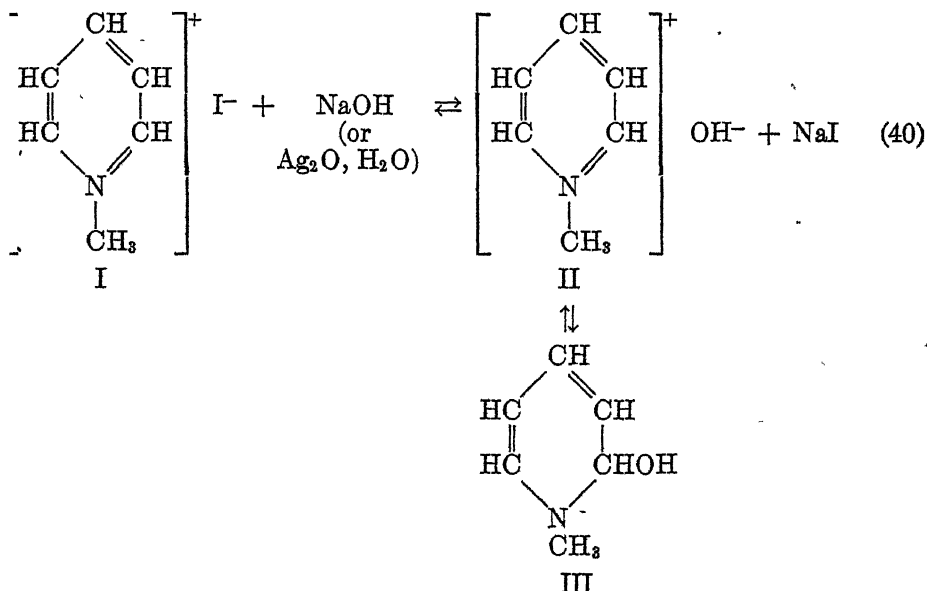
Hantzsch and Kalb (409) and Aston and Lasselle (18) consider the point of equilibrium in the reaction, II ⇌ III, to be far over on the left, because formation of the pseudo base, III, involves partial destruction of the completely conjugated system of the pyridine ring in II.

Even though large quantities of III may not be present, oxidation of pyridine methiodide in alkaline solution results in a good yield of 1-methyl-2-pyridone (IV), as shown by the equation:

$$
\begin{array}{ccc}
\text{III} & \xrightarrow[\text{or electrolytically}]{K_3Fe(CN)_6} & \text{IV}
\end{array}
\qquad (41)
$$
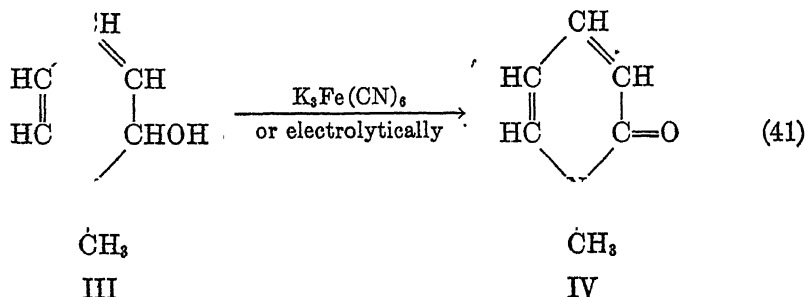
Generally, the pyridine alkiodide or methosulfate is dissolved in aqueous alkali, benzene added, and then an aqueous solution of potassium ferricyanide introduced with stirring. The N-methylpyridone (IV) dissolves in the benzene layer (188, 196, 223, 286, 295, 697). Oxidation can also be accomplished electrolytically (302, 309, 639).

The 1-alkyl-2-hydroxy-1,2-dihydropyridines (III) are cyclic ammono aquo meroacetals (see Section I, E) because of the grouping

$$
\begin{array}{c}
\text{OH} \\
/ \\
\text{—CH} \\
\backslash \\
\text{NCH}_3 \\
| \\
\text{R}
\end{array}
$$
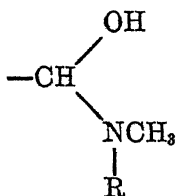
Like other meroacetals, they have as high a reactivity as the corresponding aquo aldehyde, and a much greater aldehydic reactivity than pyridine itself because of the decreased resonance in a ring that now contains only two double bonds instead of three. Related substances are treated somewhat more completely in the sections on quinoline (IV, N, 2) and isoquinoline (V, I; cotarnine).

In the past years there has been much discussion as to whether these pseudo bases have the closed-chain "carbinol" (V) or the open-chain "aldehyde" (VI) formula (371a and 458, where earlier references are given; 512). A related situation in the water system is afforded by glucose and other monosaccharides which are regarded as existing for the most part in the cyclic hemiacetal modification, in equilibrium, probably, with very small quantities of the open-chain aldehyde.

$$
\begin{array}{ccc}
\text{(V)} & \text{(VI)} & +C_2H_5OH
\end{array}
$$

$$
\cdot H_2O \quad \text{or} \quad \text{(VIII)} \tag{42}
$$

$$
\text{VII}
$$
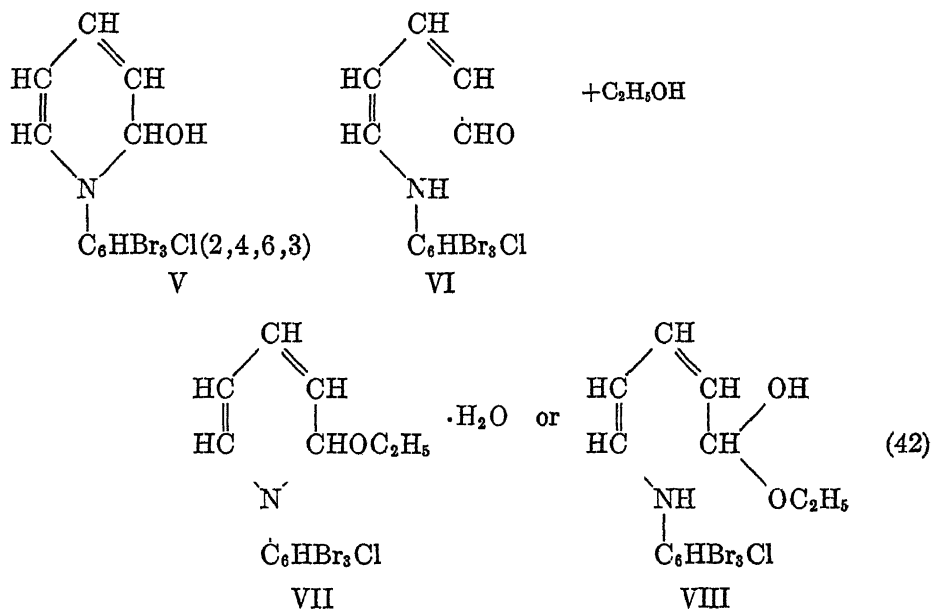
The above equation represents a reaction carried out by König (513). 2,4,6-Tribromo-3-chlorophenylpyridinium bromide was treated with alkali to give the pseudo base (V), which König considers to exist in the open-chain form, VI. Attempted crystallization from alcohol gave an "alcoholate" of the structure VII or VIII, which passed into the corresponding methoxy compound when heated with methanol. Analogous reactions of chloral alcoholate, $CCl_3CH(OH)OC_2H_5$, are mentioned in Section IV, N, 2, (a).

8. Reduction: N,N-dialkyldihydrodipyridyls, dipyridinium subhalides (tetraalkyl dipyridyl violet halides)

Reduction of N-benzylpyridinium chloride (I) with sodium amalgam gives N,N'-dibenzyltetrahydro-γ,γ'-dipyridyl (II) (cf. 280, 636, 809), in accordance with the equation:

$$
\text{(I)} \quad Cl^- \longrightarrow
$$

$$
C_6H_5CH_2N \cdots NCH_2C_6H_5 + 2NaCl \tag{42a}
$$

$$
\text{II}
$$

When alcoholic solutions of II are heated in the presence of a limited supply of air, there is formed a deep blue solution from which reddish crystals may be made to separate. Weitz (809) believes that this compound is a mixture of the quinoid dihydro-γ,γ'-dipyridyl derivative (III) with the diradical (IV) which contains two atoms of tetravalent nitrogen; recent physicochemical work indicates the correctness of the first formula, III (631, 752).

$$C_6H_5CH_2N \underset{CH=CH}{\overset{CH=CH}{\diagup\diagdown}} C=C \underset{CH=CH}{\overset{CH=CH}{\diagup\diagdown}} NCH_2C_6H_5$$

III

$$C_6H_5CH_2N \underset{CH-CH}{\overset{CH=CH}{\diagup\diagdown}} C-C \underset{CH-CH}{\overset{CH=CH}{\diagup\diagdown}} NCH_2C_6H_5$$

IV

Halogens react with III to form dialkyl halogenides of γ,γ'-dipyridyl (V). These may also be formed by oxidation of III with silver nitrate, or, less favorably, with atmospheric oxygen, followed by treatment with hydrochloric acid.

$$C_6H_5CH_2\overset{+}{N} \underset{CH=CH}{\overset{CH-CH}{\diagup\diagdown}} C-C \underset{CH=CH}{\overset{CH-CH}{\diagup\diagdown}} \overset{+}{N}CH_2C_6H_5$$

X⁻   X⁻

V

Reduction of V with sodium amalgam, or with zinc dust and glacial acetic acid, gives the blue dibenzyldihydro-γ,γ'-dipyridyl (III).

Emmert (280) heated alcoholic solutions of N,N'-dibenzyltetrahydro-γ,γ'-dipyridyl (II) with γ,γ'-dipyridyldichlorobenzylate (V, X=Cl) and obtained a deep blue or violet salt which he considers to be a quinhydrone-like compound of the constitution below (VI), and calls "tetrabenzyldipyridyl violet chloride", following suggestions of Dimroth and Frister (249). Weitz is of the opinion that it is best regarded as a free radical (VII) with one tetravalent nitrogen atom, and indeed this formula is in agreement with its behavior towards para-hydrogen (752; see, however, 631).

Cl⁻

$$C_6H_5CH_2N \underset{CH=CH}{\overset{CH=CH}{\diagup\diagdown}} C=C \underset{CH=CH}{\overset{CH=CH}{\diagup\diagdown}} NCH_2C_6H_5$$

Cl⁻

$$C_6H_5CH_2N \underset{CH-CH}{\overset{CH=CH}{\diagup\diagdown}} C-C \underset{CH-CH}{\overset{CH=CH}{\diagup\diagdown}} NCH_2C_6H_5$$

VI

$$C_6H_5CH_2N \underset{CH=CH}{\overset{CH-CH}{\Big\langle}} C-C \underset{CH=CH}{\overset{CH-CH}{\Big\rangle}} \overset{+}{N}CH_2C_6H_5 \quad Cl^-$$

VII

The dibenzyldipyridinium subhalide (VII) may also be prepared by the action of dibenzyldihydrodipyridyl (III) on an equimolar quantity of γ,γ'-dipyridyl dichlorobenzylate (V, X = Cl). Many other compounds of similar structure have been prepared and studied (280, 631, 636, 752, 809).

The mother substance of VI or VII, with hydrogen replacing the benzyl groups, was prepared by Dimroth and Frister (249) by reducing γ,γ'-dipyridyl in dilute acetic acid solution with chromous chloride.

J. PYRIDINE N-OXIDE

Colonna (174) has pointed out that the known analogy between the Schiff bases and pyridine exists also between the N-oxides of these compounds, that is to say, between the aldonitrones,

$$RCH=N \overset{\nearrow O}{\underset{\searrow R}{}}$$
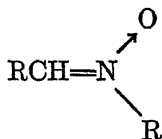
and the pyridine N-oxides:

$$C_5H_5N \rightarrow O$$

Because of the coördinate bond between nitrogen and oxygen, the former atom is positively charged, and the aldehydic properties should be enhanced in the same manner as are those of the quaternary pyridinium salts (Section II, I). This hope appears only to have been partly realized at the present time. It is reported that 2-phenylpyridine is formed by the action of phenylmagnesium bromide on pyridine N-oxide, though conditions under which this occurs are not to be found in the abstract that was available.

K. HYDROXY- AND ALKOXY-PYRIDINES, N-ALKYLPYRIDONES

2-Hydroxypyridine (1) and 2-pyridone (II) are to be considered tautomeric forms of a cyclic aquo ammono acid ester; 4-hydroxypyridine (III) and 4-pyridone (IV) are their vinylogues (cf. 71, 138, 675). 2-Hydroxypyridine is made by diazotizing 2-aminopyridine in sulfuric acid solution (108a, 156), by hydrolysis of 2-chloropyridine under acid or alkaline conditions (Section II, M, 4), by heating pyridine with dry potassium hydroxide (Section II, G), and by decarboxylating various 2-pyridonecarboxylic acids (see Beilstein, Vol. XXI, p. 43 for references). 4-Hydroxypyridine is made by heating 4-pyridonecarboxylic acids or

their salts (see Beilstein, Vol. XXI, p. 48 for references), by ammonolysis of 4-pyrone (Section II, B, 2; *cf.* 473a), and also from 4-pyridylpyridinium dichloride (497a and 497b).
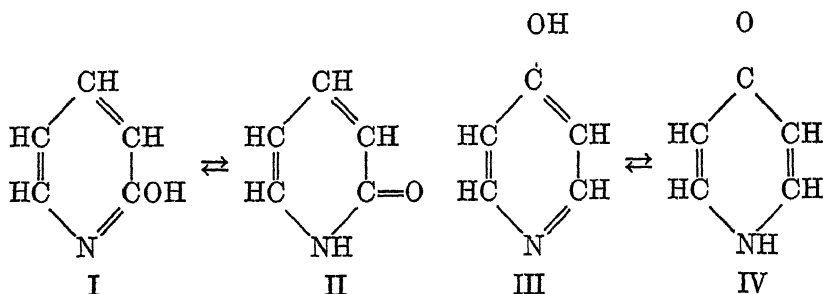
The ultraviolet absorption spectra of the *N*-alkylpyridones (see below) indicate that the aromatic ring structure of pyridine is still present (15a, 711a, 767c; *cf.* 14a, 20b, 596b, 760a).
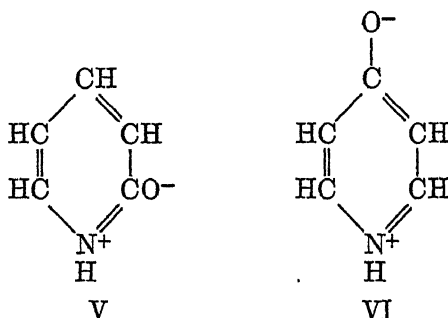
It is probable that the pyridones or hydroxypyridines are resonance hybrids of II and V or of IV and VI, in admixture with the tautomeric hydroxypyridines, I and III, and their resonant forms (VII, VIII, IX, for example).
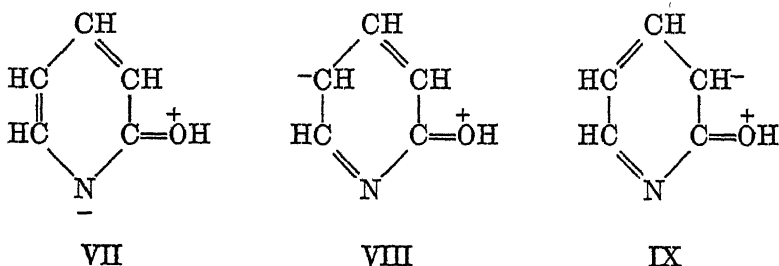
The three structures above have been patterned after the known resonant forms of phenol (83c).

While it has proven impossible to separate the chemical individuals (I and II) or (III and IV), alkyl derivatives of both are known, and are shown below:

$$X \qquad XI \qquad XII \qquad XIII$$
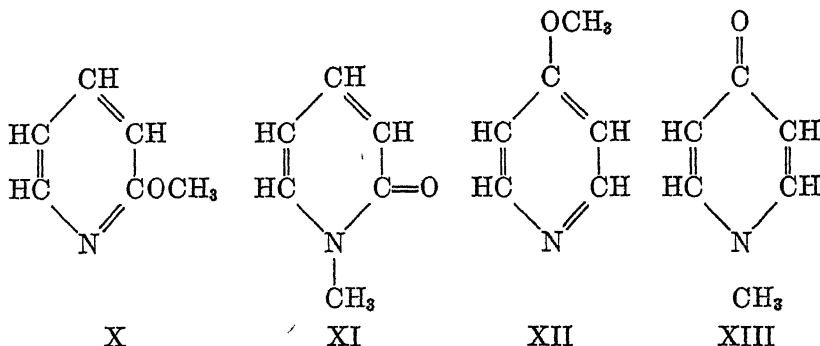
The absorption-spectra measurements referred to previously (15a, 711a, 767c) indicate that the N-alkylpyridones (XI and XIII) still retain the aromatic ring structure of pyridine and are accordingly best considered as N-methyl derivatives of the dipolar forms, V and VI.

2-Hydroxypyridine reacts with diazomethane to give 2-methoxypyridine as the sole product (596b, 597, 673a), but a mixture of 4-methoxypyridine and 1-methyl-4-pyridone is similarly obtained from 4-hydroxypyridine (597). Pure 2- and 4-alkoxypyridines are formed by the action of sodium alkoxides on the 2- or 4-chloropyridines (see Section II, M, 4). 2-Methoxypyridine (X) may also be made by shaking the silver salt of 2-hydroxypyridine with ethereal methyl iodide solution, but an almost equal amount of the isomeric N-methylpyridone (XI) is formed at the same time. 2-Ethoxypyridine is obtained, either by the reaction just described (680), or by the addition of sodium nitrite to a boiling solution of 2-aminopyridine and sulfuric acid in absolute ethanol (156).

. A reasonably pure N-methylpyridone (XI) may be prepared by shaking 2-hydroxypyridine with methyl iodide at 100°C. (678), by boiling a methyl alcoholic solution of its potassium salt with dimethyl sulfate (701), or by oxidation of pyridine iodomethylate in alkaline solution (Section II, I, 7).

The conclusion might be drawn that 2-alkoxypyridines are always formed when the silver salts of the pyridones are heated with alkyl halides, while the isomeric N-alkylpyridones are obtained by the alkylation of the potassium salts of the pyridones. Räth (697a) has, however, shown that this is not the case, since the proportion of the two forms is dependent upon other groups present in the molecule. Negative groups in the 5-position of 2-hydroxypyridine favor the production of N-alkyl derivatives. Thus, the silver salt of 2-hydroxy-5-nitropyridine, when heated with methyl iodide in methanol (8 hr. reflux) gave 15.6 per cent of 2-methoxy-5-nitropyridine (volatile with steam) and 60 per cent of N-methyl-5-nitro-2-pyridone (not volatile with steam). An 80 per cent yield of 5-iodo-N-methyl-2-pyridone may be obtained by boiling 5-iodo-2-hydroxypyridine, methyl iodide, and potassium hydroxide in absolute alcohol for 2 hr. The potassium salt of 2-hydroxy-5-nitropyridine, on the other hand, when methylated with methyl iodide in alcohol (boiled for 1.5 hr.) gives 0.8 per cent of 2-methoxy-5-nitropyridine and 83 per cent of 1-methyl-5-nitro-2-pyridone. The prepara-

tion of the 2-methoxy compound is best accomplished by heating 2-chloro-5-nitropyridine with methyl alcoholic sodium methylate.

2-Methoxypyridine is partially rearranged to the isomeric 1-methyl-2-pyridone when heated at 290°C. (600; cf. 600a). Presumably, both 2- and 4-alkoxypyridines should have labile alkoxy groups, since these substances are cyclic ammono aquo esters, but there is almost no evidence on this point. Their low reactivity is again to be ascribed to the effect of the high resonance energy of the pyridine ring.

2-Methoxypyridine, when heated with concentrated hydrogen iodide (d = 1.8) for 48 hr. at 100°C., gives methyl iodide and 2-hydroxypyridine—a hydrolysis of a cylic ammono aquo ester to a cyclic ammono aquo acid. However, the reaction is slower than the scission of a methyl ether in the Zeisel determination (389). It is reported in a patent (381a) that 2-alkoxy-5-aminopyridines are converted to 2-hydroxy-5-aminopyridine salts by heating with the hydrogen halides. Reduction of 2-methoxypyridine gives piperidine, apparently without the intermediate formation of pyridine (379) that was observed in the hydrogenation of 2-chloropyridine.

The isomeric N-alkylpyridones are also cylic ammono aquo esters, but they show practically no ketonic or ester reactivity. Thus, N-methyl-α-pyridone is not affected by hydrogen iodide at 165°C. (385). Decker (193) does, however, report that a poor yield of 1-methyl-2-benzylidene-1,2-dihydropyridine (XV) is formed by the action of benzylmagnesium chloride on 1-methyl-2-pyridone.

$$
\begin{array}{c}
\text{CH} \\
\text{HC} \quad \text{CH} \\
\text{HC} \quad \text{C=O} \\
\text{N} \\
\text{CH}_3
\end{array}
+ \; C_6H_5CH_2MgCl \; = \; \text{intermediate} \; \xrightarrow{H_2O}
$$

$$
\begin{array}{c}
\text{CH} \\
\text{HC} \quad \text{CH} \\
\text{HC} \quad \text{C}\text{—OH} \\
\quad \quad \text{CH}_2C_6H_5 \\
\text{N} \\
\text{CH}_3 \\
\text{XIV}
\end{array}
\xrightarrow{-H_2O}
\begin{array}{c}
\text{CH} \\
\text{HC} \quad \text{CH} \\
\text{HC} \quad \text{C=CHC}_6H_5 \\
\text{CH}_3 \\
\text{XV}
\end{array}
\quad (43)
$$
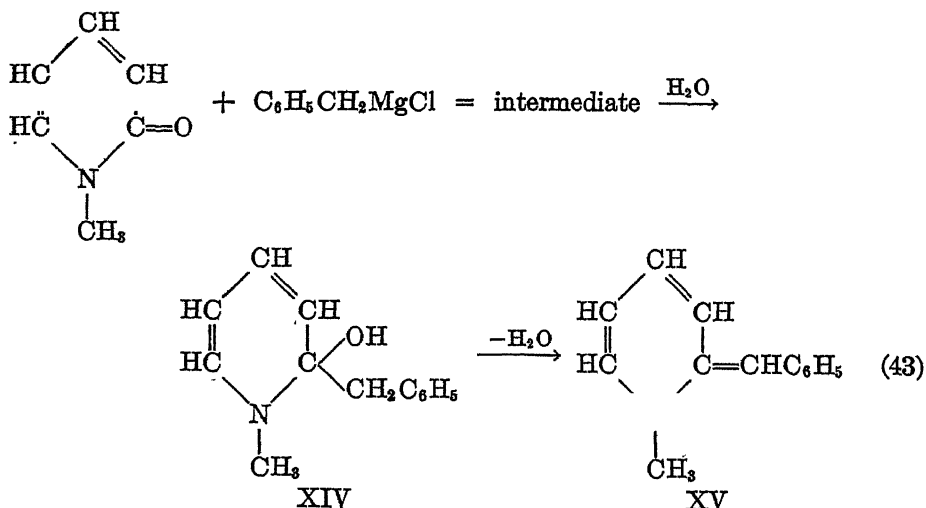
The intermediate XIV has not been isolated.

Räth (702; cf. 379) reduced 1-methyl-2-pyridone and related substances with hydrogen in the presence of a catalyst, and obtained N-alkylpiperidones of the general formula:

$$
\begin{array}{c}
\text{CH}_2\text{—CO} \\
\text{CH}_2 \quad \quad \text{NR} \\
\text{CH}_2\text{—CH}_2
\end{array}
$$
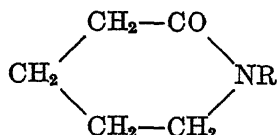
2-Pyridone (2-hydroxypyridine) was reduced with somewhat greater difficulty (200–235°C., 40 atmospheres of hydrogen) to 2-piperidone.

The N-alkylpiperidones are saturated cyclic ammono aquo esters; they may be further reduced to the corresponding cyclic ammono ether, a substituted piperidine, by heating with sodium in rigidly dried butanol (489a).

2-Phenoxypyridine, another cyclic ammono aquo ester, is prepared by heating pyridine 2-diazotate with phenol.   It isomerizes at a dull red heat to 1-phenyl-2-pyridone, and is hydrolyzed to phenol and 2-hydroxypyridine by hot concentrated hydrochloric acid (138), a reaction that may be compared to the hydrolysis of an ester to the corresponding alcohol and acid.

2,5-Dihydroxypyridine, boiled with acetic anhydride and sodium acetate, gives 2-hydroxy-5-acetoxypyridine (547a), indicating that the hydroxyl attached to the —C=N— group is less readily acetylated or, perhaps, that it is more readily removed from the 2-position when once in place. Chichibabin and Szokow (159) have thus prepared 2-acetoxypyridine, a mixed anhydride of aquo-acetic acid and the cyclic ammono aquo acid, 2-hydroxypyridine, and find that it is readily hydrolyzed by water.

<div align="center">L. AMINOPYRIDINES</div>

2-Aminopyridine is best prepared by heating pyridine with sodium amide under an inert solvent (see Section II, G), although it can also be made by the ammonolysis of 2-chloropyridine (Section II, M, 4) or by decomposition of the 2-pyridylpyridinium salts (Section II, E).

4-Aminopyridines are made in small amounts by the sodium amide method but in better yields by the ammonolysis of the 4-pyridylpyridinium salts (Section II, I, 5) or the 4-halogenopyridines (Section II, M, 7).

2-Aminopyridine (I) is a cyclic ammono acid ester, while 4-aminopyridine (III) is a vinylogue.
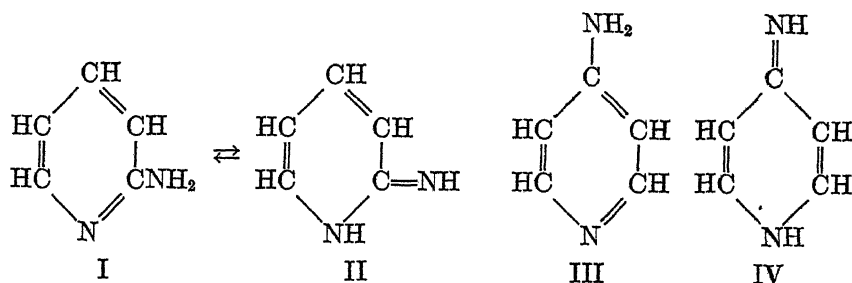
Tautomerism, in the sense of I ⇄ II and III ⇄ IV, was recognized at an early date by Chichibabin (114a, 115, 141, 142), since derivatives of all of the above are known, and particularly since bicyclic compounds including both of the two nitrogens of II in the new ring can be obtained. Perhaps the structure of the aminopyridines will be somewhat modified in the future in accordance with suggestions that have been made with regard to the hydroxypyridines and the pyridones (Section II, K).

3-Aminopyridine (for preparation see Section II, M, 6 and reference 699a) is

related to the ammonia system much as is pyridine itself; that is to say, the amino group is not particularly influenced by the double bond between the cyclic nitrogen and an adjacent carbon. The properties of an amino group in the 3-position are for this reason more like those of the amino group in aniline or other primary aromatic amines (182a; cf. 596a, 691a). While 3-aminopyridine forms a dihydrochloride, 2- and 4-aminopyridines form only monohydrochlorides (596a, 692), indicating that they are less basic. Although 3-aminopyridine can be diazotized in the usual manner, the formation of a diazo derivative of 2-aminopyridine is accomplished only by treating the sodium salt of 2-aminopyridine with amyl nitrite in ethereal solution. Direct diazotization of 2-aminopyridine in sulfuric acid solution, and also under other conditions, gives 2-hydroxypyridine (108a, 156); diazotization in hydrofluoric acid (156), in hydrochloric acid (156), or in hydrobromic acid (156, 182) gives, respectively, 2-fluoropyridine (25 per cent yield), 2-chloropyridine (not over 50 per cent), and 2-bromopyridine (87 per cent yield). Careful acidification of a solution of the diazo oxide prepared from 2-aminopyridine and mixed with potassium iodide gives 2-iodopyridine (156).

Nitration of 2-aminopyridine first gives the mixed anhydride of the ammono aquo acid ester, 2-aminopyridine, and aquonitric acid, $C_5H_4N \cdot NHNO_2$ (154). When warmed in concentrated sulfuric acid solution, isomerization to 3- and 5-nitro-2-aminopyridine occurs (139). At the same time, some 2-hydroxypyridine is formed by a process which amounts to the hydrolysis of a cylic ammono acid ester (2-aminopyridine) to a cyclic ammono aquo acid ester (2-hydroxypyridine) (139). Better yields of 2-hydroxypyridine (about 60 per cent) are obtained by boiling 2-nitraminopyridine, $C_5H_4N \cdot NHNO_2$, with acetic anhydride and glacial acetic acid, the other product being nitrous oxide, an anhydride of ammonoaquonitric acid (324).

Methylation of 2-aminopyridine by heating with methyl iodide alone gives 1-methyl-2-pyridone imide (V) (141b, 141c, 142),

$$V \qquad\qquad VI \qquad\qquad VII$$
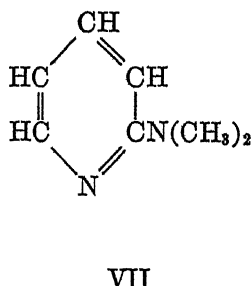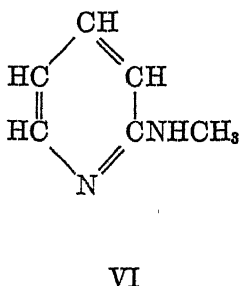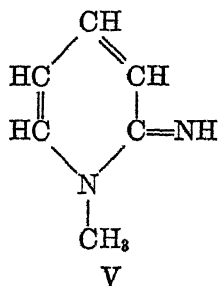
while methylation of sodium 2-aminopyridine gives monomethylaminopyridine (VI) and dimethylaminopyridine (VII). The two methylated aminopyridines can be separated by fractional distillation, after acetylation of the mixture. There is little in the literature concerning the mobility of the methylamino or dimethylamino group of the above compounds, VI and VII, but it is apparently rather low in spite of the fact that VI is a cyclic ammono acid ester, and VII is a cyclic ammono ester (140, 141, 141d, 142, 153, 158). Chichibabin and Knunianz

(140) heated 2-dimethylaminopyridine (VII) with sodium amide for some hours at 190°C. and prepared 2,6-diaminopyridine. In this process, a dimethylamino group was split off, albeit somewhat reluctantly, and 2-aminopyridine formed. Introduction of a second amino group gives 2,6-diaminopyridine. Of course, 2-dimethylamino-6-aminopyridine could be the first reaction product, for the order of the steps is unknown. The replacement of dimethylamino by amino is to be compared to the saponification of an ester.

Like 2-aminopyridine, 2,6-diaminopyridine and 2-amino-6-hydroxypyridine are mono acid bases (754a). When 2,6-diaminopyridine is heated with 70 per cent sulfuric acid on the water bath for 2 hr., one amino group is almost quantitatively replaced by hydroxyl (754a). Seide and Titov (754a) believe that the mobile amino group is attached to doubly bonded carbon, thereby making the assumption that the bonds of 2- or 2,6-substituted pyridines are sensibly static.

M. HALOGEN SUBSTITUTION PRODUCTS OF PYRIDINE

It has been previously shown that 2-chloropyridine (I) is a cyclic ammono acid chloride ester, while 4-chloropyridine (II) is its vinylogue.

I   II
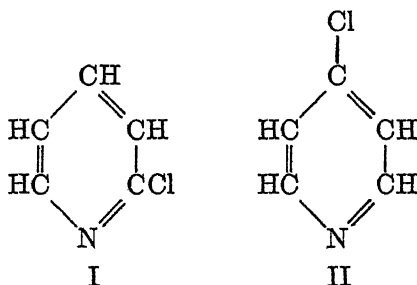
Activation of halogen in the 2- or 4-position is therefore to be expected. The reactivity of the halogen in the 3-halogenopyridines will be of the same order as in the phenyl halides.

1. Preparation

2-Chloropyridine may be made from 2-aminopyridine through pyridine 2-diazotate (see Section II, L), as well as by the action of phosgene or phosphorus pentachloride on the N-alkyl-2-pyridones (295, 672, 682, 699) or on 2-hydroxypyridine (386), in accordance with equations 44 and 45:

$$C_5H_4NOH + PCl_5 = C_5H_4NCl + HCl + POCl_3 \qquad (45)$$
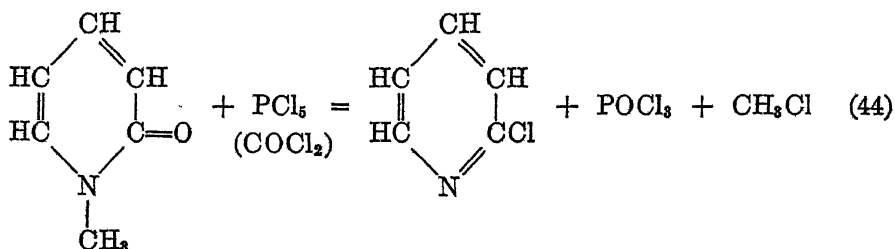
The reaction of equation 45 is the conversion of an ammono aquo acid ester to an ammono acid chloride ester. In the reaction of equation 44, a cyclic ammono aquo ester is changed to an ammono acid chloride ester, just as acetyl chloride and ethyl chloride are formed when ethyl acetate is heated at 140–150°C. with phosphorus pentachloride (602), or as benzoyl chloride is similarly prepared from methyl benzoate (21).

Direct chlorination of pyridine in the vapor phase at 270°C. results in a fairly good (31–46 per cent) yield of 2-chloropyridine, together with a smaller amount of 2,6-dichloropyridine (814f). Chlorination at the lower temperature of 200°C. gives 3,5-dichloro-, 3,4,5-trichloro-, and pentachloro-pyridines; the first named is also formed by chlorinating fused pyridine hydrochloride (715f, 814g).

3-Chloropyridine may be made from 3-aminopyridine through the diazonium salt (71a). 4-Chloropyridine is best prepared by the methods of equation 44 or 45 (303, 383a, 813b), but it may also be obtained, mixed with an isomer, by treating pyridine N-oxide with sulfuryl chloride (77a) or by the action of hydrochloric acid on 4-nitraminopyridine (500a).

2-Bromopyridine has been prepared from 2-aminopyridine through the iso-diazotate (Section II, L), or from the N-alkylpyridones in the manner of equation 44 (298). It may be made, together with 2,6-dibromopyridine, by the vapor-phase bromination of pyridine at 500°C., according to den Hertog and Wibaut (424). McElvain and Goese (567b) have modified this synthesis by preheating the bromine and pyridine vapors before they reach the reaction chamber.

Vapor-phase bromination at 300–350°C. gives 3-bromo- and 3,5-dibromo-pyridines (424; cf. 567b), but the preparation of large quantities of both of these compounds seems most readily accomplished by heating the perbromide of pyridine hydrobromide (or hydrochloride), $(C_5H_5NH)^+Br \cdot Br_2^-$, for 6 to 8 hr. at 230–250°C. (280a, 567b, 570a; cf. 106c). 3-Bromopyridine is also readily made from 3-aminopyridine through the diazonium salt (71a).

4-Bromopyridine is obtained by the action of phosphorus pentabromide and phosphorus oxybromide on 4-hydroxypyridine (813b, 814c) and by a series of reactions that start with 4-aminopyridine (814e).

The direct iodination of pyridine in the vapor phase has been accomplished (715c), though better results are obtained in the presence of an oxidizing agent, fuming sulfuric acid (715c), but even in this case the yield of 3-iodopyridine is only 18 per cent. Pentaiodopyridine may be formed in yields as high as 37 per cent by heating iodine and pyridine hydrochloride (567b, 715d). Baumgarten (41a) treated the open-chain glutacondialdehyde derivative,

$$NaOCH=CH-CH=CH-CH=N-SO_3Na$$
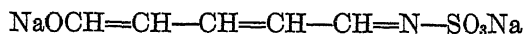
with iodine and potassium acetate, to prepare a mixture of 3-iodo- and 3,5-diiodo-pyridines, with the latter predominating. 3-Iodopyridine can of course be made from 3-aminopyridine by the usual methods (71a, 699a).

2. Instability of the 4-halogenopyridines

While the 2-halogenopyridines are stable and may be stored for some time without serious decomposition, 4-chloro- and 4-bromo-pyridines are very re-

active and therefore difficult to keep. Haitinger and Lieben (383a) commented on this instability many years ago. Wibaut and coworkers (813a, 814c) find that 4-bromopyridine turns to a solid if kept in a sealed tube overnight, and decomposes violently when an attempt is made to analyze it by the usual combustion method. 4-Chloropyridine is a little more stable, but it will slowly solidify over a period of days, perhaps in the manner of the following equations (813a):

$$\text{(45a)}$$
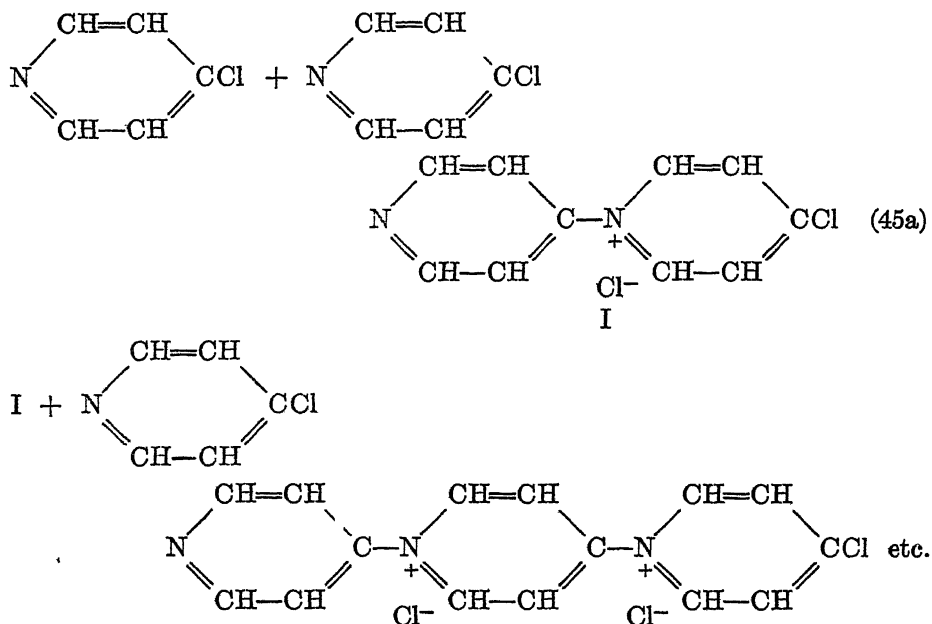
Steric factors appear to prevent the similar intermolecular condensations of the 2-halogenopyridines.

McElvain and Goese (567b), in attempting to prepare 3-bromopyridine by the method of den Hertog and Wibaut (424), found that their reaction tube became plugged periodically with a black solid, particularly if pyridine was in excess. The same solid was obtained when excess pyridine and pyridine hydrobromide perbromide were heated together (567b). Analysis of the free base obtained by adding alkali to an aqueous solution of the black mass indicated that this latter contained a repeating unit of the type
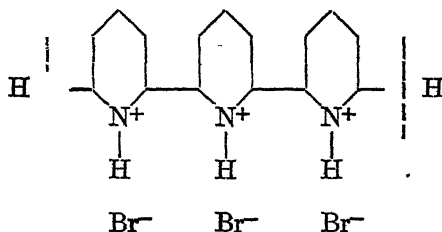
The nuclei may, of course, be united in the 2,4'- or in the 4,4'-positions. The average polymer is believed to contain four pyridine rings, indicating a possible relationship with the 2,2',2"-tripyridyl of Morgan and Burstall (627).

3. Comparison of reactivity of halogen in the 2-, 3- and 4-positions

A pentachloro-2-picoline (I) and hexachloro-2-picoline (III) mixture is partially reduced when heated with hydrogen iodide with the formation of 5-chloro-2-methylpyridine (II). The reduction has therefore affected all of the chlorine atoms except the one in the 5-position, which is the most inert (648a).
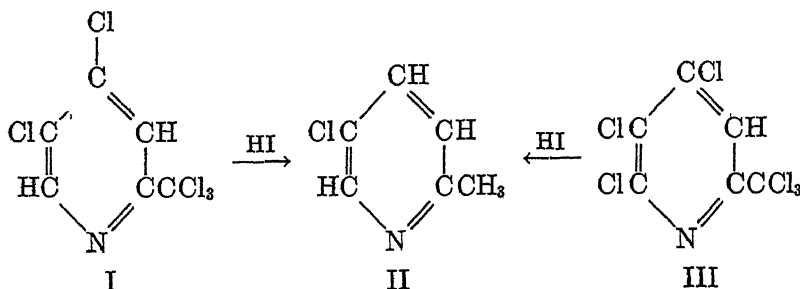
2-Chloro-5-iodopyridine is converted to 2-methoxy-5-iodopyridine by heating for 4 hr. with methyl alcoholic sodium methylate on the water bath (571b). Räth (700a) has prepared 5-halogenopyridine-2-thiols by heating 2-chloro-5-(chloro, bromo, iodo)pyridine with alcoholic potassium hydrosulfide.

It is clear that, as expected, a halogen in the 3-position is the least reactive. A definite comparison of the mobility of chlorine or bromine in the 2- or 4-position of the pyridine ring does not seem possible at the present time, since the self-condensation of the 4-(but not of the 2-)halogenopyridines may be partially explained by steric considerations. Wibaut, Bickel, and Brandon (814j) report that a poor yield of 2,6-diamino-4-bromopyridine is obtained by high-temperature ammonolysis of 2,4,6-tribromopyridine, but it is unsafe to draw conclusions from this evidence alone.

4. Reactivity of chlorine or bromine in the 2-position

2-Chloropyridine reacts with aqueous ammonia in the presence of a copper sulfate catalyst (6 hr. at 250°C.) to form 2-aminopyridine (653b). The latter may also be prepared by heating 2-chloropyridine with zinc chloride–ammonia at 220°C. (297), or by the ammonolysis of 2-bromopyridine at elevated temperatures (423a, 424a). 2-Amino-6-bromopyridine and 2,6-dibromopyridine are similarly made from 2,6-dibromopyridine (423a, 424a; *cf.* 814g), and the latter also reacts with piperidine with replacement of one or both bromines by piperidino residues (424a; *cf.* 814h).

2-Anilinopyridine, $C_5H_4NNHC_6H_5$, may be prepared by heating 2-chloropyridine with zinc chloride–aniline at 200°C. (298, 307); other aromatic amines react similarly (307). Somewhat better yields of 2-anilinopyridine are obtained by refluxing 2-chloropyridine with aniline (1.5 hr.; 93 per cent yield) (814h).

Gray (379a) prepared 4-(2'-pyridylamino)benzenesulfonamide

$$C_5H_4NNHC_6H_4SO_2NH_2\text{-}p$$

by heating *p*-aminobenzenesulfonamide with 2-chloropyridine for 15 hr. at 140°C., while Phillips (686a) made the isomeric 2-(4'-aminobenzenesulfonamido)-pyridine

$$C_5H_4NNHSO_2C_6H_4NH_2\text{-}p$$
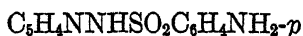
by heating 2-bromopyridine and sulfanilamide with anhydrous potassium carbonate and a trace of copper powder (180°C., 3 hr.). A potassium salt of sulfanilamide, $NH_2C_6H_4SO_2NHK$, appears to be an intermediate in this second reaction.

Replacement of the 2-chlorine is readily accomplished by heating with acid or with alkali (653a, 671). 2,6-Dibromopyridine is partly hydrolyzed to 2-bromo-6-hydroxypyridine by heating for 3 hr. with 80 per cent phosphoric acid in a sealed tube (813c); the same result may be accomplished by an aqueous alcoholic solution of alkali at 90°C. (813c). Wibaut and his coworkers (813c) point out that the rate of the acid hydrolysis is doubtless increased by the positive charge on the nitrogen of the dibromopyridine phosphate.

2-Methoxypyridine has been made by heating 2-chloropyridine with methyl alcoholic sodium methylate solution (379, 384) (see Section II, M, 4), while 2-benzyloxypyridine and many 2-aryloxypyridines have been prepared by heating the corresponding sodium alcoholate or sodium phenolate with 2-bromopyridine (710a). The 2- and 6-alkoxynicotines and 2- and 6-aryloxynicotines are similarly formed from the 2- or 6-halogenonicotines (106a).

den Hertog and Wibaut (424a) prepared 2-ethoxy-6-bromopyridine by heating 2,6-dibromopyridine with sodium hydroxide in alcohol for 4–5 hr. The 2,6-diethoxypyridine was formed only at higher temperatures (6 hr. at 160°C.).

Pyridine-2-thiol is the product of the action of an alcoholic solution of potassium hydrosulfide on 2-chloropyridine (586) or 2-iodopyridine (372a). 2-Chloropyridine can be successfully used in a modified Grignard reaction (650a; *cf*. 129, 413a, 424a). Picolinonitrile (2-cyanopyridine) is readily obtained by heating 2-chloropyridine with cuprous cyanide (182). It is tentatively reported that 2,6-dibromopyridine is catalytically reduced to pyridine in alkaline solution in the presence of nickel (814j). 2-Chloropyridine may be hydrogenated to pyridine and then to piperidine (379).

5. *2-Chloro-5-nitropyridine: activating effect of the —C=N— linkage*

2-Chloro-5-nitropyridine is made by the general methods of equations 44 and 45 from the *N*-alkyl-5-nitro-2-pyridones or from 2-hydroxy-5-nitropyridine (106d, 572, 686a, 699). The chlorine is activated, not only by the cyclic —C=N— group, but also by the nitro group in the para position with respect to it. As the result of comparative experiments, Mangini and Frenguelli (572) have concluded that chlorine in 2,5-dinitrochlorobenzene is the more reactive, indicating that the halogen is affected more by an ortho nitro group than by —C=N— in the same position.

The high mobility of the chlorine in 2-chloro-5-nitropyridine makes it a

valuable intermediate in the synthesis of pyridine derivatives. Catalytic hydrogenation, best with a palladium–calcium carbonate catalyst, not only reduces the nitro group but also replaces the chlorine with hydrogen to give 3-aminopyridine, (72a, 72b), which is otherwise not readily available. Reduction in a similar manner in alcoholic sodium hydroxide solution yields 2-alkoxy-5-aminopyridines (72a).

2-Hydrazino-5-nitropyridine is formed quantitatively from 2-chloro-5-nitropyridine and hydrazine in aqueous solution (572, 698a). It is converted by catalytic oxidation to 3-nitropyridine (702d), which is obtained in very poor yield by direct nitration of pyridine. Short boiling with alcoholic solutions of primary aromatic amines or with piperidine replaces the 2-chlorine with substituted amino groups (572; cf. 742a). p-(5'-Nitro-2'-pyridylamino)benzenesulfonamide may be made by heating sulfanilamide with 2-chloro-5-nitropyridine for 15 min. at 170°C. (686a).

5,5'-Dinitro-2,2'-dipyridyl sulfide (788a; cf. 788) and 5-nitropyridine-2-thiol (106d) have been prepared individually by the action of thiourea on 2-chloro-5-nitropyridine under different conditions.

6. Reactivity of halogen in the 3-position

3-Bromo- and 3,5-dibromopyridines are found to be much less reactive than the 2- and 2,6-halogenated pyridines described in the preceding paragraphs. Reduction of 3-bromopyridine with hydrazine hydrate, in the presence of palladized calcium carbonate, gives 3,3'-dipyridyl (106c) and high-temperature ammonolysis with aqueous ammonia and copper sulfate yields 3-aminopyridine (424a, 570a). 3-Methoxypyridine is formed by heating 3-bromopyridine for 2 days with alcoholic potash at 150°C. (496, 807). 3-Cyanopyridine (nicotinonitrile) may be prepared by heating 3-bromopyridine with cuprous cyanide at 165–170°C. (1 hr.; 567c).

High-temperature ammonolysis of 3,5-dibromopyridine by concentrated aqueous ammonia in the presence of copper sulfate (30 hr., 200°C.) gives 3-amino-5-bromopyridine (424a, 585b) or 3,5-diaminopyridine (424a, 570a).

Attempted formation of the Grignard reagent from 3-bromo- or 3,5-dibromopyridine was unsuccessful (413a), though 3-pyridyllithium was prepared from 3-bromopyridine and butyllithium in ether (373b, 772b).

7. Reactivity of 4-chloro- and 4-bromopyridines

Reactions with the above-named compounds should be carried out shortly after their preparation, to avoid the self-condensations that have been previously described (see II, M, 2).

4-Aminopyridine is obtained either by heating 4-chloropyridine with zinc chloride–ammonia (4–5 hr. at 220–230°C.) (279) or by heating 4-bromopyridine with concentrated aqueous ammonia for 8 hr. at 200°C. (814d). 4-Amino- and 4-anilinopyridines can be prepared from 4-pyridylpyridinium dichloride (497a, 497b).

Renshaw and Conn (710a) have made 4-butoxy-, 4-phenoxy-, 4-cresoxy-

pyridines and related "ethers" by heating 4-pyridylpyridinium dichloride with alcohol or phenol, in accordance with the original method of Koenigs and Greiner (497a, 497b).

4-Methoxypyridine has been prepared by heating 4-chloropyridine with methyl alcoholic sodium methylate at 100°C. (388; cf. 710a), and pyridine-4-thiol is similarly obtained, but at higher temperature (140°C.), from 4-chloropyridine and alcholic potassium hydrosulfide (500).

3,4,5-Trihalogenopyridines, when heated with alkali hydrosulfides, give 3,5-dihalogenopyridine-4-thiols (260c), which may be oxidized to the corresponding 4-sulfonic acids (260a, 260c). The latter may also be prepared by heating the 3,4,5-trihalogenopyridines with alkali bisulfite (260a). The sulfonic acid group in the 4-position is mobile, and may be replaced by an amino or phenyl-amino group when heated with ammonia or aniline, respectively (260b).

When 4-chloropyridine is heated in a sealed tube for a long time with concentrated hydrogen iodide solution, 4-iodopyridine hydroiodide and pyridine hydroiodide are formed successively, the latter requiring the higher temperature (383a). Catalytic hydrogenation of 2,6-diamino-4-bromopyridine with nickel in alkaline solution gives 2,6-diaminopyridine (814j).

N. PYRIDINECARBOXYLIC ACIDS

The effect of the —C=N— group in activating a substituent in the 2- or 4-position of the pyridine ring is generally rather pronounced, as has been shown in the preceding section. Pyridine-2-carboxylic acid (picolinic acid) is analogous to an α-keto acid of the water system, while pyridine-4-carboxylic acid (isonicotinic acid) may be regarded as a vinylogue. The literature does not allow us to differentiate between their stabilities toward heat, since the melting points increase uniformly with distance from the nitrogen, that of picolinic acid being 138°C., of nicotinic acid 232°C., and of isonicotinic acid 317°C. While picolinic acid is a water–ammonia analogue of an α-ketonic acid, and nicotinic acid is similarly related to a β-keto acid, their stability is of course greater than expected because of the pyridine ring resonance.

However, pyridine-2,3-dicarboxylic acid (quinolinic acid), when heated to 180–190°C., melts with gas evolution, and passes into pyridine-3-carboxylic acid (nicotinic acid) (108, 429). All pyridine di- or poly-carboxylic acids with one carboxyl in the 3-position similarly lose a 2- or 4-carboxyl to form nicotinic acid; the 2-carboxyl is the most readily lost (108, 571a, 647). The double bond between carbon and nitrogen in the pyridine ring therefore has some influence, particularly on carboxyl in the 2-position, and to a lesser degree on carboxyl in 4.

2-Pyridylacetic acid, $C_5H_4NCH_2COOH$, is analogous to a β-keto acid, such as acetoacetic acid, CH_3COCH_2COOH, since the —C=N— of the ring is analogous to carbonyl. Like acetoacetic acid, carbon dioxide is lost rather readily on heating, in this case only to 50–60°C. in aqueous solution. The methyl ester, like acetoacetic ester, is stable (646).

A rather peculiar reaction, dependent upon the proximity of carboxyl to the —C=N— of the ring, is reported by Ashworth, Daffern, and Hammick (16,

264). When 2-picolinic acid, and also quinoline-2-carboxylic acid or isoquinoline-1-carboxylic acid, are decarboxylated thermally in the presence of aldehydes or ketones, 2-pyridyl(2-quinolyl, 1-isoquinolyl)carbinols are formed. Typical reactions are the following:

Quinoline-2-carboxylic acid (quinaldic acid) (2.5 g.) and benzophenone (25 g.) are heated for 2 hr. at 175°C., giving 3 g. of diphenyl(2-quinolyl)carbinol:

$$
\begin{array}{c}
CH=CH \\
C_6H_4 \qquad\qquad OH \\
N= \quad \dot{C}-C-C_6H_5 \\
C_6H_5
\end{array}
$$
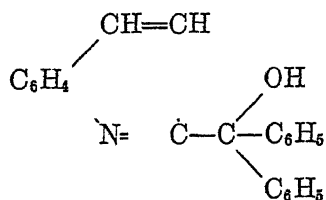
Picolinic acid (5 g.) and benzaldehyde (30 g.), heated for $1\frac{1}{4}$ hr. at 140°C., gave 3 cc. of phenyl(2-pyridyl)carbinol:

$$
\begin{array}{c}
CH \\
HC \qquad CH \\
H\ddot{C} \qquad CCH(OH)C_6H_5 \\
N
\end{array}
$$
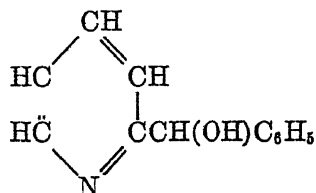
These reactions are specific for α-imino acids such as the two above. The suggestion is made that the anion radicals produced when these acids lose carbon dioxide contain a modified "cyanide ion" structure, $(N=C)^-$, which adds to the carbonyl group as does the cyanide ion in the familiar cyanohydrin reaction. The parallel equations are the following:

$$
(N=C)^- + C_6H_5CHO \rightarrow C_6H_5CH \begin{array}{c} O^- \\ \diagdown \\ C=N \end{array} \quad \xrightarrow{H^+} \quad C_6H_5CH \begin{array}{c} OH \\ \diagup \\ C=N \end{array} \qquad (46)
$$

$$
\begin{array}{c} \text{Phenyl(2-pyridyl)} \\ \text{carbinol} \end{array}
$$

$$
C_6H_5CHO + CN^- \longrightarrow C_6H_5CH \begin{array}{c} O^- \\ \diagdown \\ CN \end{array} \quad \xrightarrow{H^+} \quad C_6H_5CH \begin{array}{c} OH \\ \diagup \\ CN \end{array} \qquad (47)
$$
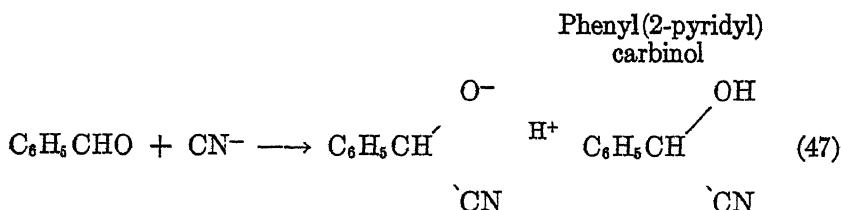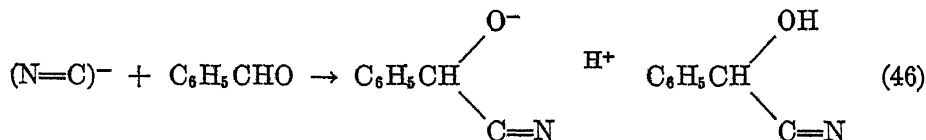
III. Some Cyclic Oxygen Compounds Related to Pyridine and Quinoline

Cyclic oxonium salts are known in considerable numbers, but it is impossible adequately to review their chemistry in an article devoted to heterocyclic nitro-

gen compounds. Representatives of a few of the principal types are shown below, together with their nitrogen analogues:

I
Pyrylium chloride

II
Benzopyrylium
chloride

III
Flavylium chloride

IV
Xanthylium chloride

V
Pyridine

VI
Methylpyridinium iodide

VII
VIII
Methylpyrylium salts
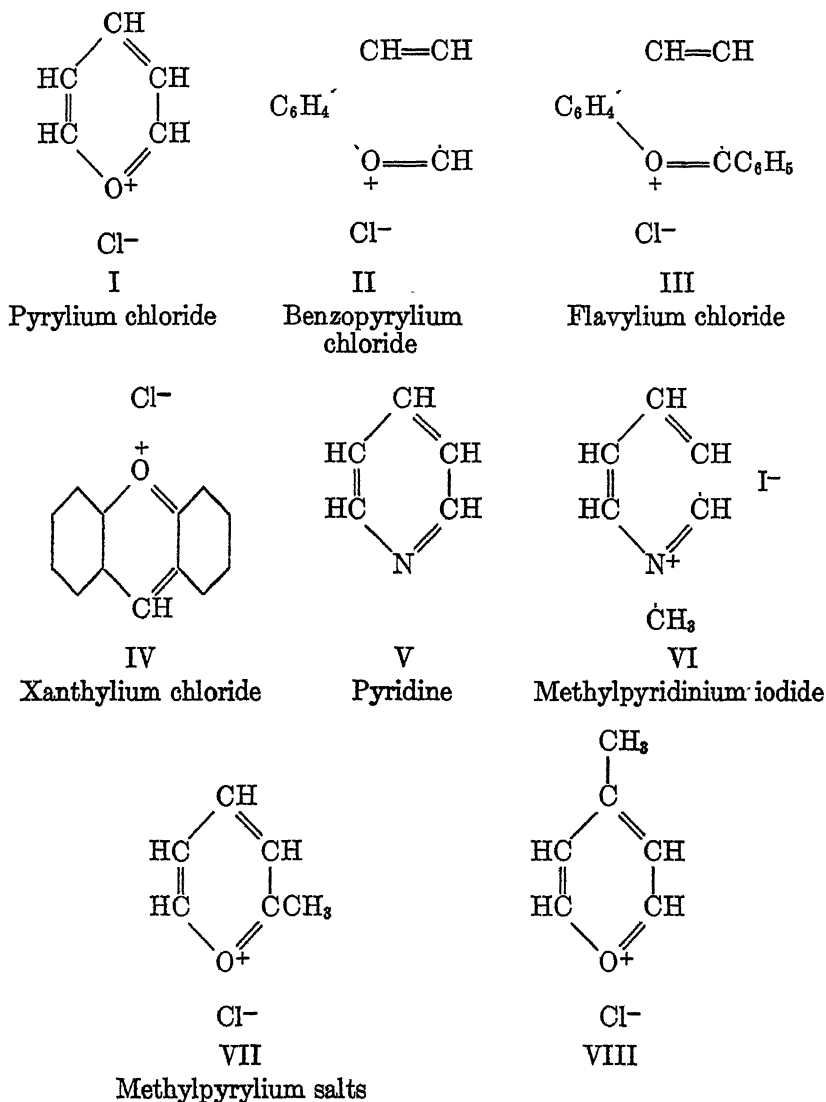
Each of the oxygen compounds listed contains a $-CH\overset{+}{=}O-$ or $CH_3-\overset{|}{C}\overset{+}{=}O-$ group and so can be regarded as a type of cyclic aquo aldehyde (I, II, III, IV) or ketone (VII, VIII). It is true that the cyclic structure is possible only if the oxygen is positively charged; one may accordingly speak of the positive ions of (I–IV) or of (VII, VIII) as aldehydic or ketonic cations, respectively. The positive charge, which must be redistributed in some measure to the o- and p-positions of the ring by resonance, should result in an increase of the carbonyl re-

activity in transformations which concern basic reagents, as has proven to be the case with the related pyridinium (VI), quinolinium, and isoquinolinium salts (see Sections II, I; IV, N; V, G). The structural and chemical resemblance between oxonium salts and quaternary ammonium salts related to methylpyridinium iodide (VI) has been very clearly pointed out by Dilthey, Decker, and their coworkers (212, 247).

The formulas of the pyrylium, benzopyrylium, and xanthylium salts given above are not universally accepted, but are believed by some (*cf.* 425) to be the following (carbonium and carbenium theories):

<div style="text-align:center">

CH   •CH

HC   CH   HC   ·CH

HC   CH•   Cl⁻ or HC   CH   Cl⁻

O   O

IX   X

</div>
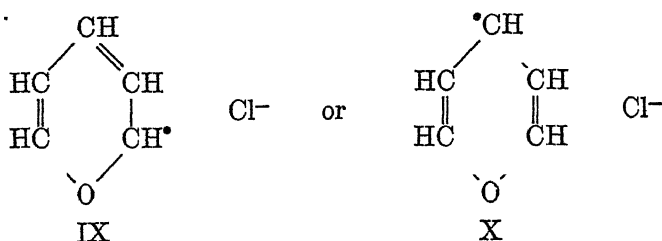
The anionic charge is localized for the most part on the ortho or para position, as indicated by the dots. The corresponding bases (XI and XII) should have the structures:

<div style="text-align:center">

                       OH

CH   CH

HC   CH   HC   CH

HC   CHOH or HC   CH

    O   O

XI   XII

</div>
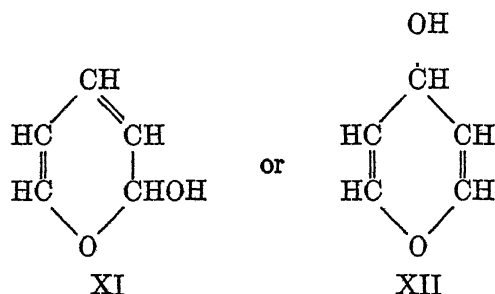
The former, XI, is merely a cyclic hemiacetal; the latter, XII, its vinylogue. The salt (IX) might be compared with monochloromethyl methyl ether, $ClCH_2OCH_3$, or with dichloromethyl ether, $ClCH_2OCH_2Cl$, which contains chlorine intermediate in reactivity between that of an alkyl halide, RCH_2X, and an acid halide, $RCOX$. Both of the halogen-substituted methyl ethers can easily be converted to formaldehyde or its derivatives by the action of water, alcohol, or ammonia, and therefore can be said to act as a source of formaldehyde. Otherwise stated, the compounds that are obtained by replacing the hydroxyl group of a hemiacetal, $RCH(OH)OR'$, with halogen still have aldehydic reactivity.

A methyl group in the 2-, 4-, or 6-position of a pyrylium salt and in the 2- or 4-position of a benzopyrylium salt resembles the same group in a methyl ketone in that styryl derivatives are readily formed by the action of aromatic aldehydes (82, 106, 246, 401, 415, 416, 744, 804, 804a; *cf.* 79). A partial equation is the following:

$$C—CH_3 + C_6H_5CHO \longrightarrow H_2O + \quad C—CH=CHC_6H_5 \quad (48)$$
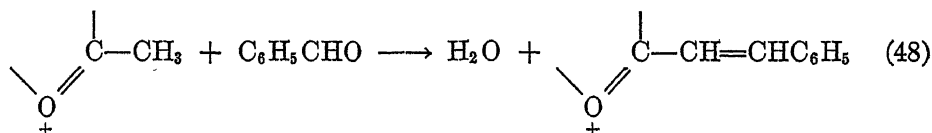
Styrylpyrylium and styrylxanthylium salts can of course also be made by ring closure reactions (*cf.* 80).

Methylene in the 4-position of a tetrahydroxanthylium salt appears more reactive than a 9-methyl group, since Borsche and Wunder (82a) report the following condensation:

$$(49)$$
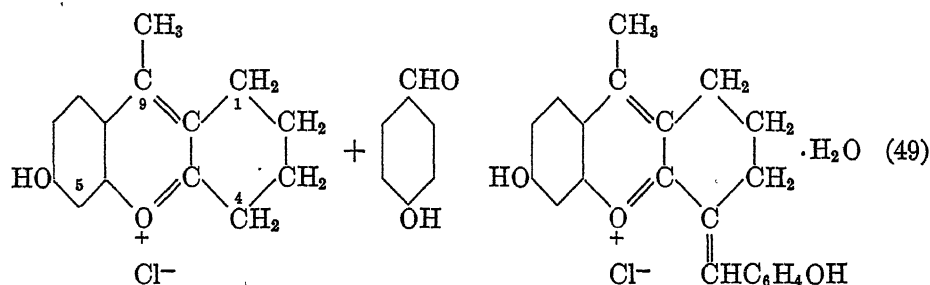
The reviewer was unable to find record of the ammonolysis of a simple benzopyrylium (II) or flavylium (III) salt to the corresponding quinoline. Perhaps in the very voluminous literature on these salts, such transformations have been described. Ammonia in aqueous solution supposedly first precipitates a pseudo base or pyranol (XIII):

$$(50)$$
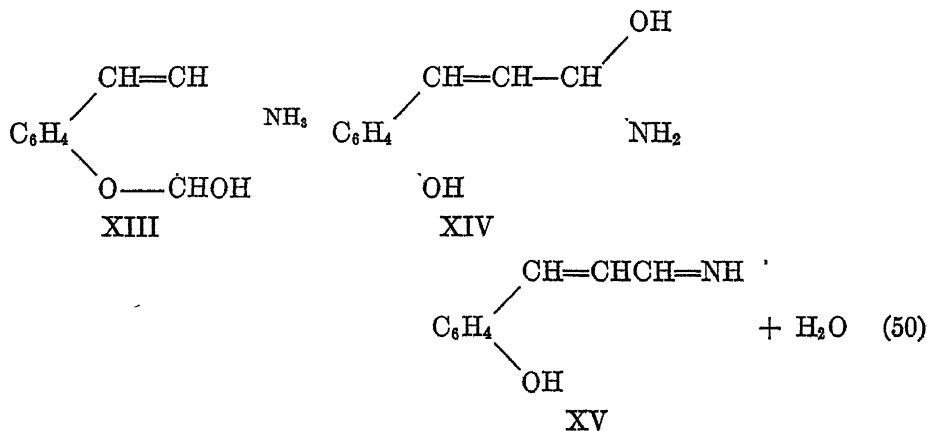
If ammonolysis occurs at this stage and the ring opens to form the hypothetical substance XIV, which will lose water to give XV, ring closure will give a quinoline derivative only if the phenolic hydroxyl is lost, a reaction that would be difficult. On the other hand, ammonolysis of a pyrylium salt will be much easier, since the loss of water from the (not isolated) intermediate (XVI), with resulting ring closure, involves a much more mobile enolic hydroxyl.

$$
\begin{array}{c}
\text{CH} \\
\diagup \quad \diagdown \\
\text{HC} \qquad \text{CH} \\
\parallel \qquad\quad | \\
\text{RC} \qquad \text{CR} \\
\diagdown \quad \diagup \\
\overset{+}{\text{O}} \\
\end{array}
\ \text{Cl}^- \quad + \ 2NH_3 \ = \
\begin{array}{c}
\text{CH} \\
\diagup \quad \diagdown \\
\text{HC} \qquad \text{CH} \\
| \qquad\quad | \\
\text{RC} \qquad \text{CR} \\
| \qquad\quad \parallel \\
\text{OH} \qquad \text{NH} \\
\end{array}
\quad + \ NH_4Cl \qquad (51)
$$

$$
\text{XVI}
$$

$$
\text{XVI} \ - \ H_2O \ = \
\begin{array}{c}
\text{CH} \\
\diagup \quad \diagdown \\
\text{HC} \qquad \text{CH} \\
\parallel \qquad\quad | \\
\text{R}\overset{..}{\text{C}} \qquad \text{CR} \\
\diagdown \quad \diagup \\
\text{N} \\
\end{array}
$$
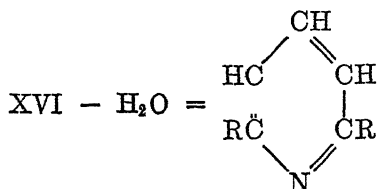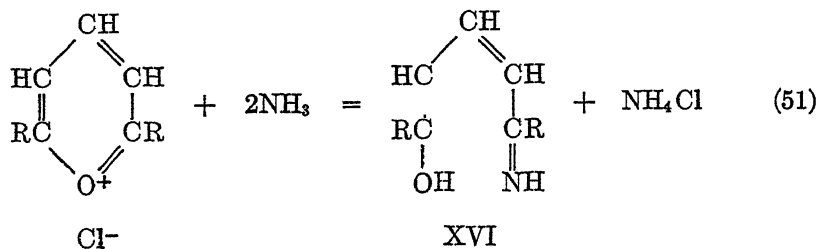
For similar reasons, the γ-pyrones are easily ammonolyzed to γ-pyridones Section II, B, 2), while quinolones or carbostyryls apparently cannot be made in a like manner from the related coumarins:

$$
C_6H_4
\begin{array}{c}
\diagup\text{CH}\!=\!\text{CH} \\
\diagdown\,\text{O}\!-\!\overset{\cdot}{\text{C}}\!=\!\text{O}
\end{array}
$$

$$
\text{XVII}
$$
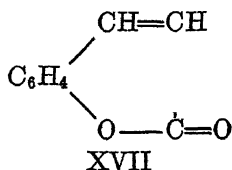
Ring opening with ammonia probably would give o-hydroxycinnamamide, $C_6H_4(OH)CH\!=\!CHCONH_2$, rather than o-aminocinnamic acid, $C_6H_4(NH_2)CH\!=\!CHCOOH$, although neither transformation seems to be on record. Coumarin (XVII) is an internal ester, and ammonolysis of esters usually gives an acid amide. While o-aminocinnamic acid can be converted to 2-hydroxyquinoline (carbostyryl), though not too readily (see Section IV, G), o-hydroxycinnamic acid apparently cannot be by the action of ammonia.

Isoquinoline derivatives can, on the other hand, be made without difficulty by the ammonolysis of isocoumarin or isocoumarincarboxylic acids (equations 145, 147; Section V, A, 4).

$$
C_6H_4
\begin{array}{c}
\diagup\text{CH}\!=\!\text{CH} \\
\diagdown\,\text{CO}\!-\!\overset{\cdot}{\text{O}}
\end{array}
\ + \ NH_3 \ \xrightarrow[\text{C}_2\text{H}_5\text{OH}]{120\text{--}130^\circ\text{C.}}\
C_6H_4
\begin{array}{c}
\diagup\text{CH}\!=\!\text{CHOH} \\
\diagdown\,\text{CONH}_2
\end{array}
\quad -H_2O
$$

$$
\text{XVIII}
$$

$$
C_6H_4
\begin{array}{c}
\diagup\text{CH}\!=\!\text{CH} \\
\diagdown\,\text{CO}\!-\!\overset{\cdot}{\text{N}}\text{H}
\end{array}
\ \rightleftarrows \
C_6H_4
\begin{array}{c}
\diagup\text{CH}\!=\!\text{CH} \\
\diagdown\,\text{C}\!=\!\overset{\cdot}{\text{N}} \\
\ \quad\text{OH}
\end{array}
\qquad (52)
$$
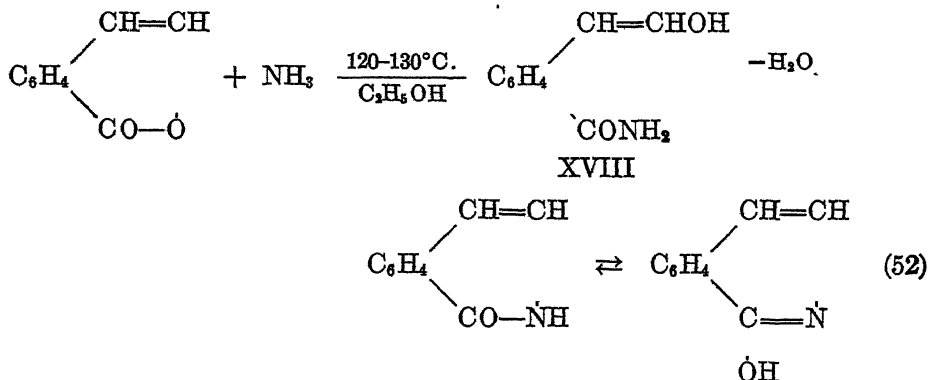
The enolic hydroxyl of the assumed intermediate (XVIII) will be more readily replaced by a substituted amino group (ammonolysis) than is the phenolic hydroxyl of o-hydroxycinnamamide.

Expanded cyclic aquo acetals: xanthydrol

As many investigators have pointed out, xanthydrol (IV) is the pseudo base corresponding to the xanthylium salts (I); it is best made by reducing xanthone (II).

$$Cl^-$$
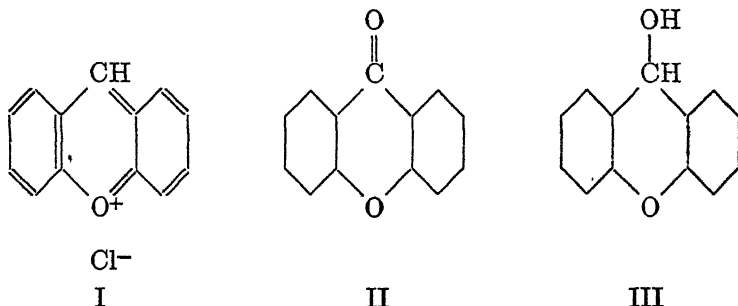
I   II   III

Since the grouping, $—CH—C{=}COR$, of xanthydrol (III) is equivalent to

$$—CH\overset{OH}{\underset{OR}{\diagdown}}$$
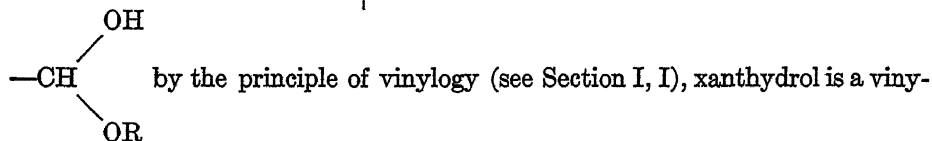
by the principle of vinylogy (see Section I, I), xanthydrol is a vinylogue of an aquo hemiacetal, or, perhaps more simply, an expanded hemiacetal, if one uses the terminology of Ingold. Xanthone (II) is an expanded aquo ester.

A large number of compounds with reactive methylene, or even with active hydrogen, condense readily with xanthydrol, as in the illustrative equation:

$$+ CH_2(COOH)_2 \longrightarrow \qquad\qquad + H_2O \qquad (52a)$$
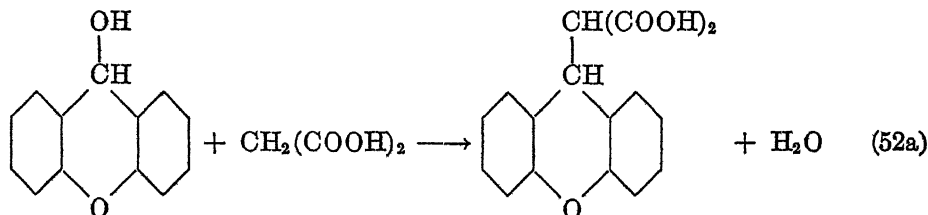
Among the substances that react in accordance with equations similar to 52a are the following: malonic acid (318a), malonic ester, acetylacetone, cyanoacetic esters, benzoylacetic esters, acetoacetic ester (318a, 318b, 318i), α- and β-substituted indoles (441c), thiophene and thionaphthene (8b), and pyrrole (441b).

Aromatic amines and acid amides readily form xanthyl derivatives when treated with xanthydrol, in the manner of the following equations:

$$\text{[xanthydrol with OH, CH, O]} + RCONH_2 \longrightarrow \text{[xanthyl derivative with NHCOR, CH, O]} + H_2O \quad (52b)$$
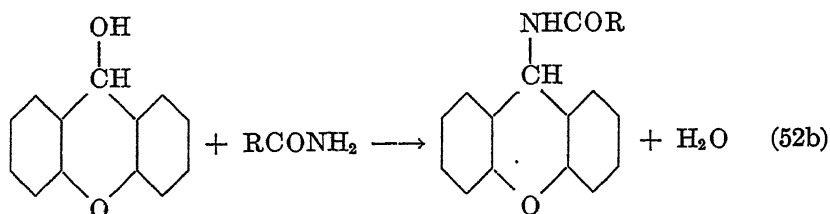
Primary aromatic amines thus form mono- or di-xanthyl derivatives, depending upon conditions.

$$\text{[xanthydrol with OH, CH, O]} + RNH_2 \xrightarrow{-H_2O} \text{[derivative with NHR, CH, O]}$$

$$\text{and} \quad \left[\text{[structure with CH, O]}\right]_2 NR \quad (52c)$$
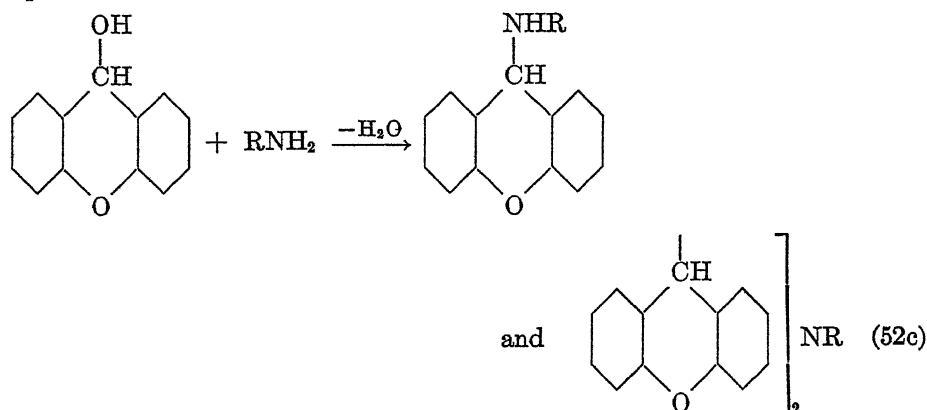
Among the nitrogenous compounds that react with xanthydrol are the following: fatty acid amides (318h), urea (8a, 318h; a dixanthyl derivative is formed), substituted ureas (2a), thiourea (318h), hydroxylamine (318a, 318g), semicarbazide (261a, 318a, 318g), indole and α- and β-substituted indoles (318f, 441c), isatin (441c), saccharin (285a), antipyrine (285a), veronal and other barbiturates (285a), aniline, toluidine, o-nitroaniline, diphenylamine, acetanilide, naphthylamine, etc. (2a, 318a), sulfamide and sulfonamides (819a).

Xanthydrol is used in the quantitative analysis of urea (8a, 318f) and many other compounds.

Dinaphthopyranol (sym-dibenzoxanthydrol) behaves chemically in the same manner as xanthydrol (318a, 318b, 318i).

IV. QUINOLINE

Quinoline (I) is best regarded as a cyclic ammono aldehyde ether, whose reactivity should be somewhat greater than that of pyridine because of the activating influence of the fused benzene ring. Substituents in the 4- and 2-positions will have approximately the same function (principle of vinylogy, transmission of effects along a conjugated chain; Section I, I).

$$C_6H_4 \begin{array}{c} CH=CH \\ \diagup \\ \diagdown \\ N=\ =CH_2 \end{array} \qquad C_6H_4 \begin{array}{c} CH=CH \\ \diagup \\ \diagdown \\ N==\overset{\cdot}{C}CH_3 \end{array} \qquad C_6H_4 \begin{array}{c} CH=CH \\ \diagup \\ \diagdown \\ N==\overset{\cdot}{C}C_6H_5 \end{array}$$

Cyclic aldehyde ether   II   III
                       Cyclic ketone ethers

$$CH_3$$
$$C\!=\!CH$$
$$C_6H_4$$
$$N\!=\!CH$$

IV

$$C_6H_5$$
$$C\!=\!CH$$
$$C_6H_4$$
$$N\!=\!CH$$

V

Vinylogues of ketone ethers

$$CH\!=\!CH$$
$$C_6H_4$$
$$N\!=\!\overset{\cdot}{C}OH$$

VI

Cyclic ammono aquo
acid ester

$$CH\!=\!CH$$
$$C_6H_4$$
$$N\!=\!CNH_2$$

VII

Cyclic ammono
acid ester

$$CH\!=\!CH$$
$$C_6H_4$$
$$N\!=\!CCl$$

VIII

Cyclic ammono acid
chloride ester

$$CH\!=\!CH$$
$$C_6H_4$$
$$N\!=\!COC_2H_5$$

IX

Cyclic ammono aquo ester

$$CH\!=\!CH$$
$$C_6H_4$$
$$N\!=\!CN(CH_3)_2$$

X

Cyclic ammono ester

A. SYNTHESIS OF QUINOLINE AND ITS DERIVATIVES

Since there is available a recent review concerning quinoline (584), the discussion of the methods of synthesis may be limited to the reactions that are the most readily interpreted in accordance with the point of view of the present article.

1. The Friedländer synthesis

$$C_6H_4\overset{\text{CHO}}{\underset{\text{HN}_2\text{-}o}{\Big\langle}} \ + \ \underset{O=\overset{|}{C}-R}{\overset{CH_3}{|}} \ \xrightarrow[\text{bases}]{\text{dilute}} 2H_2O \ + \ C_6H_4\overset{CH=CH}{\underset{N=\overset{\cdot}{C}R}{\Big\langle}} \tag{53}$$
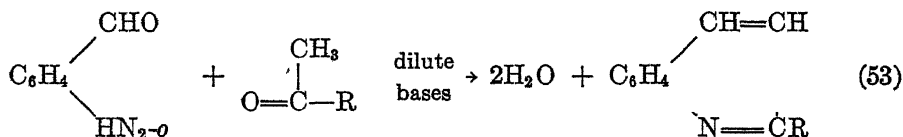
There are two distinct reactions involved: a Claisen reaction between the aldehyde group and the active methyl of the ketone, and an ammonolysis of the carbonyl group of the ketone by a substituted ammonia. The type of ammonolysis represented above is familiar as the method by which Schiff bases (ammono aldehyde ethers) are formed, and the Friedländer synthesis therefore indicates quinoline to be a cyclic Schiff base. Open-chain Schiff bases, RCH=NR', have long been known to have aldehydic properties (321, 608, 609, 780, 782); in fact, the anils of o-aminobenzaldehyde, $C_6H_4(NH_2)CH=NR$, have recently been used by Borsche and Ried (81d) in a modification of the Friedländer synthesis.

2. The Pfitzinger synthesis

$$COONa$$
$$|$$
$$C=O$$

$$\underset{Isatin}{\overset{\displaystyle \text{CO}}{\underset{\displaystyle \text{NH}}{\big\diagup\!\!\diagdown}}\!\!\text{CO}} \xrightarrow{\text{NaOH}} \underset{\text{Sodium isatinate}}{C_6H_4\underset{NH_2}{\overset{\displaystyle C=O}{\diagup\diagdown}}} \xrightarrow[\text{strong NaOH, heat}]{C_6H_5COCH_3}$$

$$COONa$$
$$|$$
$$C=CH$$

$$C_6H_4 \qquad\qquad (54)$$

$$N=CC_6H_5$$

Sodium salt of cinchophen
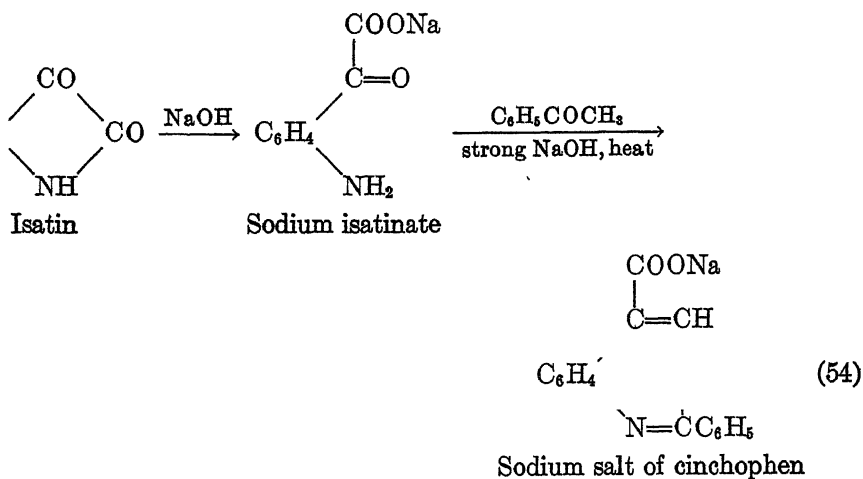
This reaction is very similar to the Friedländer synthesis, but uses the more readily available isatin as a starting material instead of the comparatively unstable o-aminobenzaldehyde.

3. The Skraup synthesis

Quinoline and its derivatives are formed by heating a primary aromatic amine, the corresponding nitro compound (or arsenic acid, etc.), glycerol, and concentrated sulfuric acid, with the occasional addition of ferrous sulfate or boric acid to prevent too violent a reaction at the beginning. Clarke and Davis (162) with the latter modification have prepared quinoline in 84–91 per cent yields. Catalysts, such as thorium oxide, metavanadic acid, or vanadium pentoxide (184b, 234) and copper sulfate (474b), have been recommended, and the use of acetylated amines is believed by Manske (582, 583) to offer distinct advantages in some cases. 2-Ethylquinoline and several 3-alkyl- and -arylquinolines have been made by using substituted glycerol ethers in a modification of the Skraup synthesis (184a, 234, 799f, 806).

It is generally assumed that acrolein (I) is an intermediate in the Skraup synthesis as generally carried out (cf. 73a, 288b, 584). The inability to obtain significant yields of quinoline (IV) from the product of reaction of acrolein and aniline (109, 490, 573) may be construed as evidence of a negative character for some other intermediate, or it may only mean that acrolein must be generated in situ to avoid side reactions.

$$\underset{NH_2}{\bigcirc} + CH_2=CHCHO = \underset{II}{\underset{NH}{\bigcirc}\overset{OHC}{\underset{CH_2}{\diagup}}\underset{|}{\overset{}{CH_2}}} \xrightarrow{-H_2O}$$

$$
\begin{array}{ccc}
\text{III} & \xrightarrow[\text{from } C_6H_5NO_2]{(O)} & \text{IV}
\end{array}
\tag{55}
$$

$$
CH_2=CHCHO + C_6H_5NH_2 \rightarrow CH_2=CHCH=NC_6H_5 \xrightarrow{\ C_6H_5NH_2\ }
$$

$$
\text{V}
$$

$$
\text{VI} \xrightarrow{-C_6H_5NH_2} \text{III} \xrightarrow[C_6H_5NO_2]{(O)} \text{IV} \tag{56}
$$
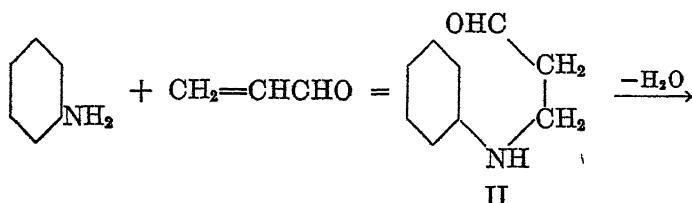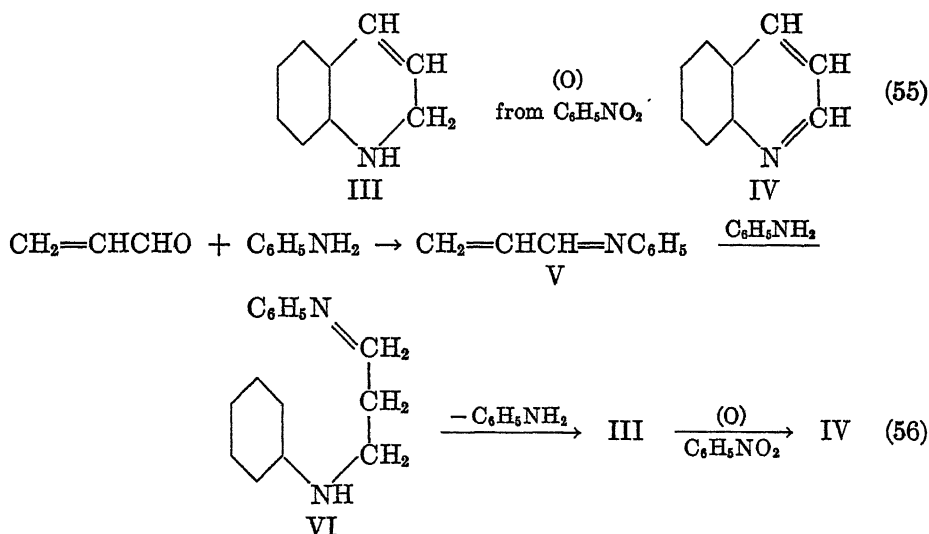
In equation 56 the Schiff base, acrolein aniline (V), adds aniline to form VI, which by loss of aniline is cyclized to dihydroquinoline (III), The addition of aniline to a carbon-to-carbon double bond conjugated with —CH=N— is reasonable, since Bruson and Riener (102, where earlier references are given; 105c, 656) have carried out many related reactions with acrylonitrile, $CH_2=CHC\equiv N$. Whether II or VI or some other compound (73, 506a, 584) is the true intermediate in the Skraup synthesis will depend upon whether or not it is formed in sufficient concentration under the conditions of the experiment. The fact that Schiff bases may be hydrolyzed by heating with dilute acids might argue against V or VI (702c).

Regardless of the mechanism assumed, the cyclization is the result of the loss of water or of aniline by attack of the aldehydic terminal of a side chain on a ring hydrogen in the ortho position. Whether this is preceded by isomerization of II or V to an enol or to the related enamine is not known (cf. 775).

4. The Döbner–(von) Miller synthesis

When aldehydes or polymerized aldehydes, such as paraldehyde, are refluxed for several hours with concentrated hydrochloric acid, quinoline derivatives are formed in accordance with the over-all equations:

$$
C_6H_5NH_2 + 2CH_3CHO = C_6H_4 \underset{N=CCH_3}{\overset{CH=CH}{\big\langle}} + 2H_2O + (2H) \tag{57}
$$

$$
C_6H_5NH_2 + 2CH_3CH_2CHO = C_6H_4 \underset{N=CCH_2CH_3}{\overset{CH=CCH_3}{\big\langle}} + 2H_2O + (2H) \tag{58}
$$

The alkyl in position 2 always has one more carbon than the one in position 3.

As will be seen further on, a dihydroquinoline is usually believed to be intermediate in the reaction. It is generally thought that this is reduced by the hydrogen (=2H) to a tetrahydroquinoline (*cf.* 445), but Mills and coworkers (614) were unable to isolate any compound of this type in a Döbner–Miller synthesis of quinaldine from acetaldehyde, aniline, hydrochloric acid, and zinc chloride. They obtained instead a mixture of ethylaniline and butylaniline, in approximately equal amounts, apparently as the result of a reduction of ethylideneaniline, $CH_3CH=NC_6H_5$, and crotonylideneaniline, $CH_3CH=CHCH=NC_6H_5$, respectively. The latter is probably obtained from the former by the action of acetaldehyde. At the same time there was isolated a smaller amount of 6-ethylquinaldine.

One mechanism proposed long ago by Döbner and von Miller is the following (255a; *cf.* 73, 288b, 607, 608, 609a):

$$CH_3CHO + C_6H_5NH_2 \qquad CH_3CH=NC_6H_5 + H_2O \qquad (57)$$
$$\text{I}$$

$$2CH_3CH=NC_6H_5 = \underset{\underset{\text{II}}{\overset{|}{CH_2CH=NC_6H_5}}}{CH_3CHNHC_6H_5}$$

$$\text{II} \qquad \xrightarrow{- C_6H_5NH_2} \qquad \text{III}$$

$$(2H) + \qquad\qquad \text{IV} \qquad\qquad (57)$$

Ethylideneaniline (I), a Schiff base, is an ammono aldehyde ether. It undergoes an aldol condensation to give II, whose relationship to ordinary aldol is made apparent by replacing OH with NHC_6H_5 and $=O$ with $=NC_6H_5$ in the formula $CH_3CH(OH)CH_2CHO$. Cyclization is effected by loss of aniline to give dihydroquinaldine (III), which has not been isolated since it gives quinaldine and tetrahydroquinaldine by dismutation, or else it loses two hydrogens to the Schiff base (I) to form ethylaniline, $CH_3CH_2NHC_6H_5$, as in the experiments of Mills (614). More recently, Jones and collaborators (268, 372, 446) and Mills, Harris, and Lambourne (614) have given evidence for believing that the "aldol bases" of Miller and Plöchl (609b) are intermediates in the Döbner–Miller synthesis.

These compounds (VII) may be regarded as formed from open-chain amino-aldehydes (VI) in accordance with the equation:

$$
\begin{array}{ccc}
\text{VI} & & \text{VII}
\end{array}
\tag{58}
$$

The similarity to the last step of the Skraup reaction is apparent, since cyclization takes place because of the attack of the terminal aldehydic group of a side chain upon an ortho hydrogen of the ring. This is also true of the reaction of equation 57. An intermediate similar to the "aldol base" (VII) is of course possible in the Skraup synthesis, and it is unnecessary to say that enolization precedes ring closure.

The precursor of the aldol base, possibly VI, may be formed by the hydrolysis of the ammono aldol (II), with replacement of $=NC_6H_5$ by $=O$, or by the aldol condensation of ethylideneaniline (I) with aquoacetaldehyde in accordance with the equation:

$$CH_3CHO \;+\; CH_3CH{=}NC_6H_5 \longrightarrow CH_3CH(OH)CH_2CH{=}NC_6H_5$$

$$\text{VIII}$$

$$
\text{or} \quad
\underset{\substack{|\\ CH_2CHO\\ VI}}{CH_3CHNHC_6H_5}
\tag{58a}
$$
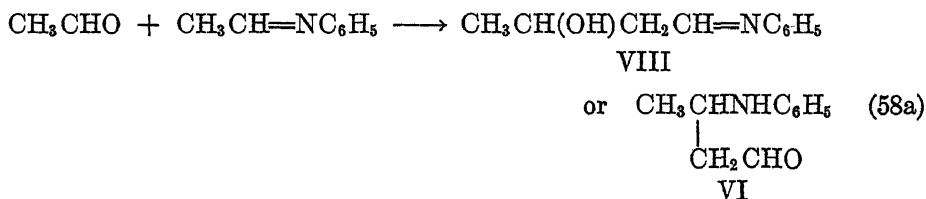
By loss of water, VIII passes into crotonylideneaniline (IX), $CH_3CH{=}CHCH{=}NC_6H_5$, the reduction of which gives the butylaniline obtained by Mills and his students (614). Cyclization of IX should proceed in accordance with equation 58b to give 4-methyl-3,4-dihydroquinoline (X).

$$
\begin{array}{ccccc}
\text{IX} & & \text{X} & \xrightarrow{-2H} & \text{XI}
\end{array}
\tag{58b}
$$
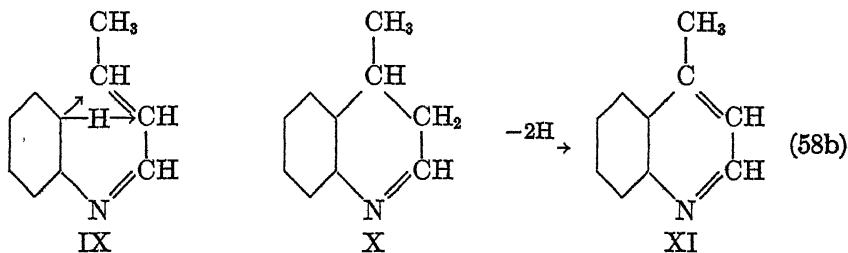
Dehydrogenation of X will give lepidine (XI), but no 4-substituted quinolines appear ever to have been isolated in the Döbner–Miller synthesis. This is an excellent indication that ring closure goes most readily if the end of the side chain is a group of aldehydic or ketonic function, such as —CHO, —CH=NC_6H_5, —CH(OC_2H_5)_2, —COR, or —CH(NR_2)_2 (cf. equations 57, 58).

It is reasonable to say that the actual intermediate in any quinoline synthesis must be capable of formation in concentration sufficiently great to account for the speed of the overall reaction. Therefore, reactivities being approximately equal, the intermediate is the one that is most likely to be present under the prevailing conditions of acidity and temperature. It is possible that both II and VI or VII will contribute toward the formation of quinaldine, though doubtless to unequal extents, since Schiff bases may be hydrolyzed in acid solution (702c).

Roberts and Turner (713) have given a good discussion of the effect of substituents upon the ring closure of the Döbner–Miller and related syntheses.

5. The Combes synthesis

The fundamental Combes synthesis (175) is best illustrated by the formation of 2, 4-dimethylquinoline in the manner of the following equation:

$$C_6H_5NH_2 + CH_3COCH_2COCH_3 = H_2O + CH_3COCH_2C(=NC_6H_5)CH_3$$

I   II

Acetylacetone   Monoanil of acetylacetone

(59)
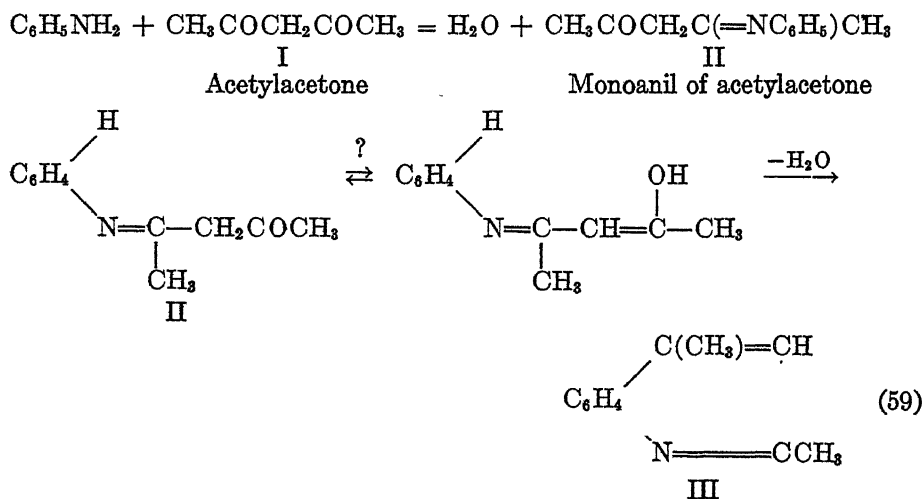
Factors that influence this synthesis have been discussed by Roberts and Turner (712).

6. The Döbner reaction (Döbner's cinchoninic acid synthesis)

A substituted cinchoninic acid (quinoline-4-carboxylic acid) is formed by heating an aromatic amine with pyruvic acid and an aldehyde (253, 254), generally in alcoholic solution. The preparation of cinchophen (2-phenylquinoline-4-carboxylic acid) proceeds in accordance with the following equation:

$$C_6H_5NH_2 + C_6H_5CHO + CH_3COCOOH \rightarrow$$

$$+ 2H_2O + (H_2) \quad (60)$$
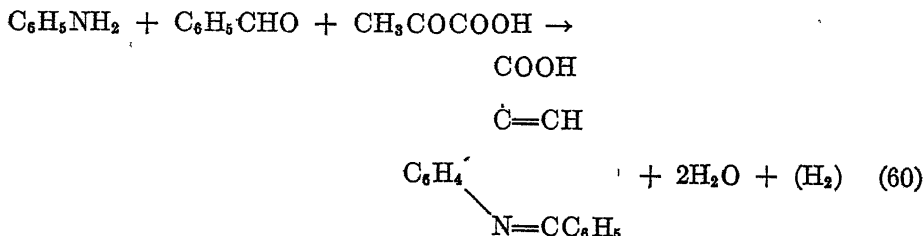
The hydrogen is not liberated as gas, but reduces the cinchoninic acids to their tetrahydrides, or the Schiff base formed from the amine and aldehyde to the corresponding secondary amine. Perhaps the most satisfactory mechanism is the one proposed by Ciusa and Muṣajo (161a), and shown below:

$$C_6H_5CHO + C_6H_5NH_2 = H_2O + C_6H_5CH{=}NC_6H_5$$
$$I$$

$$C_6H_5N{=}CHC_6H_5 + CH_3COCOOH = C_6H_5NHCHCH_2COCOOH$$
$$\underset{C_6H_5}{|}$$

$$I \qquad\qquad II \qquad\qquad III$$
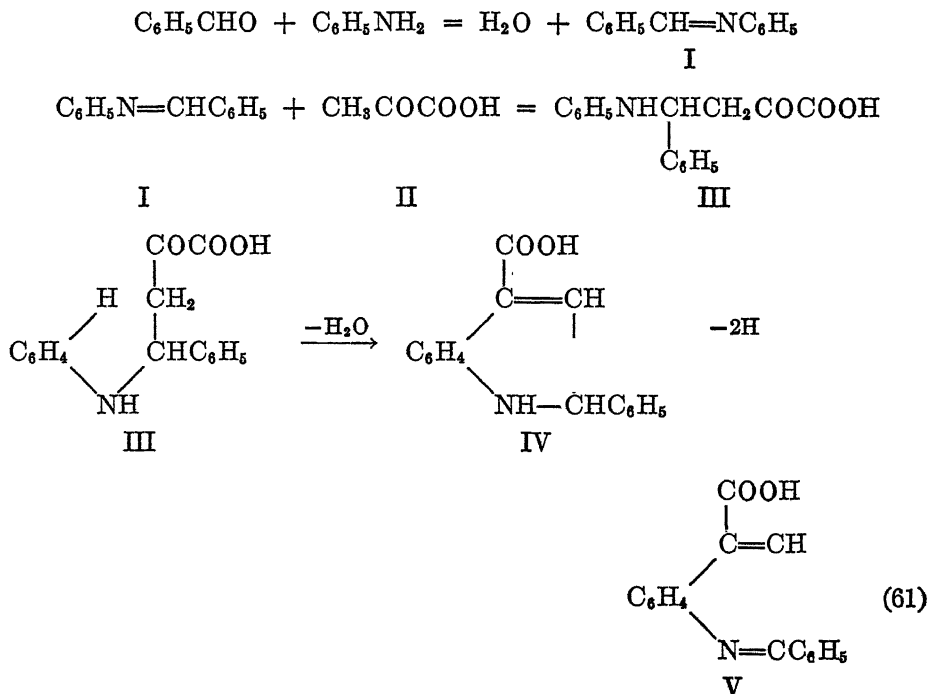
The first step represents the formation of a Schiff base, benzylideneaniline which, as an ammono aldehyde ether, undergoes an aldol condensation with pyruvic acid (II) to give the intermediate, III. This is cyclized by loss of water to the dihydrocinchophen (IV), which is oxidized at its own expense to form cinchophen (V) and its tetrahydride. Since the amount of the latter is always less than that of the unreduced V, some of the Schiff base (I) is reduced to the corresponding secondary amine, benzylaniline. Written in this manner, the Döbner reaction bears rather close relationship to the Skraup, Döbner–Miller, and Combes syntheses.

Carrara (110) formulates the Döbner reaction in a somewhat more complex fashion, to take account of the large yields of resin and of reduced Schiff base. In one experiment, pyruvic acid (40 g.) was added dropwise to a boiling solution of aniline (67 g.) and benzaldehyde (76 g.) in 1200 cc. of alcohol. From the approximately 100 g. of resin was isolated 80–90 g. of benzylaniline. The yield of cinchophen was only 6–7 g.

7. The synthesis of lepidones

Acetoacetic ester and aniline react to form acetoacetanilide (I, II), which is readily cyclized to lepidone (III, IV) by warming with concentrated sulfuric

acid on the water bath (483a, 657). Lepidone may readily be converted to 2-chlorolepidine by the action of phosphorus halides, and this in turn may be reduced to lepidine (540, 606; *cf.* 51). Some modifications and improvements of the original Knorr method have been described (6, 606, 606a, 629). Equations follow.

$$CH_3COCH_2COOC_2H_5 + C_6H_5NH_2 \quad \xrightarrow[130-140°C.]{3-4 \text{ hr.}}$$

$$CH_3COCH_2CONHC_6H_5 \rightleftarrows CH_3C(OH)=CHCONHC_6H_5$$
$$\text{I} \qquad\qquad\qquad\qquad \text{II}$$

$$\begin{array}{ccc}
\text{HO—CCH}_3 & \text{CH}_3 & \text{CH}_3 \\
\text{H} \;\; \text{CH} & \text{C=CH} & \text{C=CH} \\
C_6H_4 \quad CO & -H_2O = C_6H_4 & \rightleftarrows C_6H_4 \qquad\qquad (62) \\
\text{H} & \text{NHCO} & \text{N=COH} \\
\text{II} & \text{III} & \text{IV}
\end{array}$$
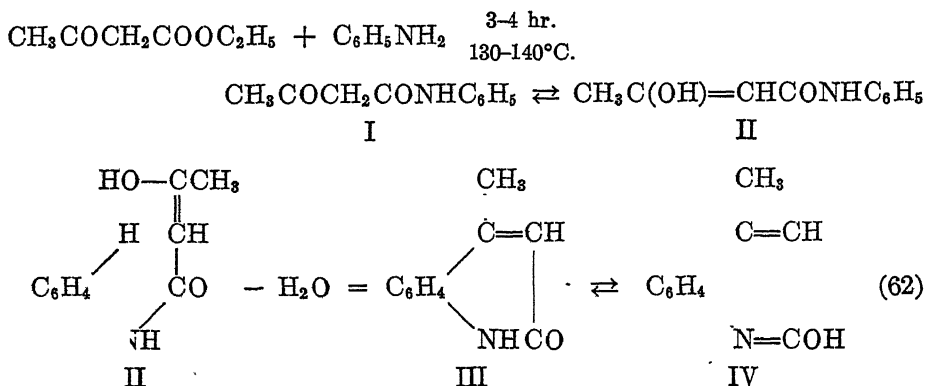
It is to be noted again that cyclization occurs as a result of the attack of the ketonic end of a side chain upon an ortho ring hydrogen.

8. The synthesis of quinaldones

The isomeric quinaldones (such as 2-methyl-4-hydroxyquinoline) are made by heating β-phenyliminobutyric acid esters, or their derivatives, to about 240°C. (176a, 176b, 485, 774), in the manner expressed by the following equations:

$$CH_3COCH_2COOCH_3 + C_6H_5NH_2 \xrightarrow[\text{in cold}]{\text{about 2 days}}$$

$$CH_3C(=NC_6H_5)CH_2COOCH_3 \quad (176b)$$
$$\text{I}$$
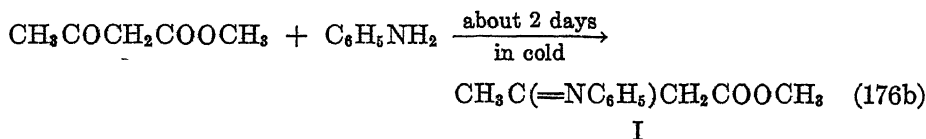
$$\text{I} - CH_3OH \text{ (short heating at 240-250°C.)} \rightarrow$$

$$\begin{array}{cc}
\text{CO—CH}_2 & \text{C(OH)=CH} \\
C_6H_4 & C_6H_4 \qquad\qquad (63) \\
\text{N= =CCH}_3 & \text{N——CCH}_3
\end{array}$$
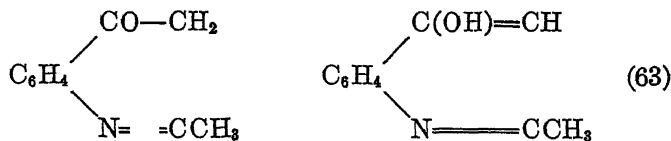
Lions, Hughes, and Ritchie (373a, 441a) have recently modified the original method of Conrad and Limpach in several details.

9. The synthesis of quinolines by the action of acetylene on aromatic amines

Acetylene and ammonia gas react over a heated contact catalyst to form pyridine derivatives, as well as acetonitrile and other substances, in a reaction discovered by Chichibabin (126) and later elaborated in the patent literature (see Section II, B, 7). It has been found in recent years that acetylene similarly reacts with aniline and other aromatic amines when warmed in the presence of

catalysts to give substituted quinolines. Kozlov and coworkers thus report that quinaldine may be made in accordance with the equations (523, 527, 528, 534):

$$C_6H_5NH_2 + CH\equiv CH \xrightarrow[50°C.]{Cu_2Cl_2} CH_3CH\!\!=\!\!NC_6H_5$$

<div align="center">I</div>

$$2CH_3CH\!\!=\!\!NC_6H_5 = CH_3\underset{\underset{CH_2CH=NC_6H_5}{|}}{CHNHC_6H_5}$$

<div align="right">(64)</div>

<div align="center">I   II</div>

$$II - C_6H_5NH_2 - (2H) \xrightarrow{heat} C_6H_4\underset{`N\!\!=\!\!CCH_3}{\overset{CH=CH}{\diagup}}$$ (see equation 57)

<div align="center">III</div>
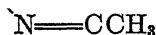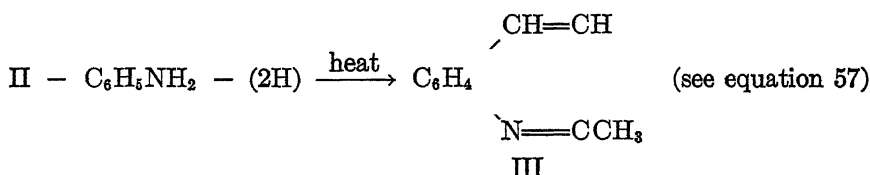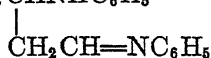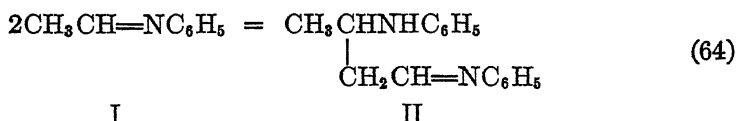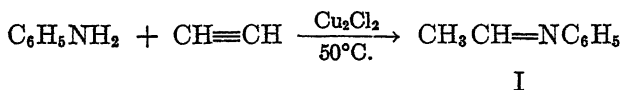
Aniline adds catalytically to acetylene to form the ammono aldehyde ether, ethylideneaniline (I), much as water reacts with acetylene in the presence of mercuric salts to give acetaldehyde. The ethylideneaniline then dimerizes by a process related to the ordinary aldol condensation, and cyclization occurs as in the Döbner–Miller synthesis of equation 57. Hydrogen is, of course, not liberated as a gas, but appears in the form of various reduced organic compounds, such as tetrahydroquinaldine. Silver nitrate, mercuric chloride, mercuric bromide, and mercuric iodide may be used as catalysts in place of the cuprous chloride. The dimeric alkylideneanilines (II) may be isolated as intermediates, but presumably require higher temperatures for conversion to quinaldines than are used in the initial condensation of acetylene with aniline.

N-Ethylaniline and acetylene react similarly to give quinaldine, indole, ethane, and hydrogen or, rather, products of reduction of the organic matter that is available (546). Kozlov and Golod (529) greatly lowered the amount of tetra-hydroquinaldine formed along with the quinaldine of the reaction of equation 64 by the use of nitrobenzene. A number of other references to this synthesis are listed (287, 521–534 inclusive, 654, 659a).

A variant of the above has been described by Kozlov (521, 523), who heated aniline, benzaldehyde, and acetylene for some hours and obtained 2-phenyl-quinoline in accordance with the following equations:

$$C_6H_5NH_2 + C_6H_5CHO = C_6H_5CH\!\!=\!\!NC_6H_5 + H_2O$$

$$C_6H_5NH_2 + CH\equiv CH = CH_3CH\!\!=\!\!NC_6H_5$$

$$C_6H_5CH\!\!=\!\!NC_6H_5 + CH_3CH\!\!=\!\!NC_6H_5 \rightarrow C_6H_4\underset{\underset{C_6H_5}{\underset{|}{NHCHCH_2CH=NC_6H_5}}}{\overset{H}{\diagup}} \rightarrow$$

<div align="center">I   II</div>

<div align="center">III</div>

$$\underset{\text{IV}}{C_6H_4 \diagdown \diagup \begin{matrix} CH = CH \\ | \\ N = CC_6H_5 \end{matrix}} + C_6H_5NH_2 + (2H) \quad (65)$$
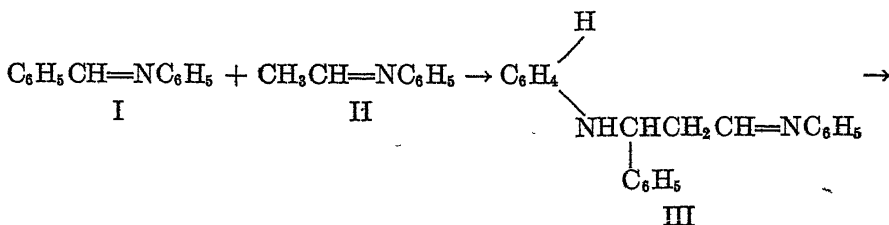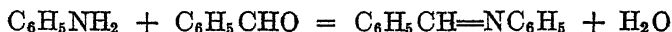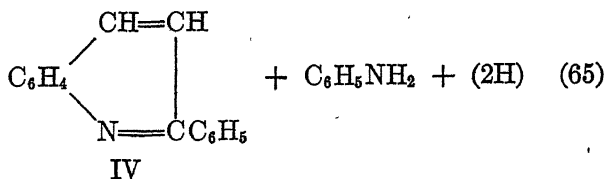
The ammono aldehyde ethers, benzylideneaniline (I) and ethylideneaniline (II), react with each other in the sense of the aldol condensation to give III, just as in Ciusa's mechanism for the Döbner cinchoninic acid synthesis (Section IV, A, 6).

Some years previous to the work described above, Chichibabin and Oparina condensed acetaldehyde and paraldehyde with aniline in the presence of aluminum oxide at elevated temperatures, and obtained a mixture of quinoline bases whose chief constituent was lepidine, 4-methylquinoline (122, 147).

B. RING OPENINGS OF QUINOLINE AND ITS RELATIVES; OXIDATIONS

From the quinoline ring openings that have been published, there are selected the following examples:

(a) 2-Aryl- or 2-alkyl-quinolines, when oxidized by potassium permanganate, give acyl derivatives of anthranilic acid, in accordance with the scheme below, which represents the formation of benzoylanthranilic acid from 2-phenylquinoline (257; *cf.* 177, 799d):

$$C_6H_4 \diagdown \diagup \begin{matrix} CH=CH \\ | \\ N=CC_6H_5 \end{matrix} \quad -\!\!-\!\!-\!\!\begin{matrix} OH \\ \overline{} \\ OH \end{matrix} \xrightarrow[\text{KMnO}_4]{\text{(O)}}$$

$$C_6H_4 \diagdown \diagup \begin{matrix} COOH \\ \\ N=CC_6H_5 \\ | \\ OH \end{matrix} \quad \rightleftarrows \quad C_6H_4 \diagdown \diagup \begin{matrix} COOH \\ \\ NHCOC_6H_5 \end{matrix} \quad (66)$$
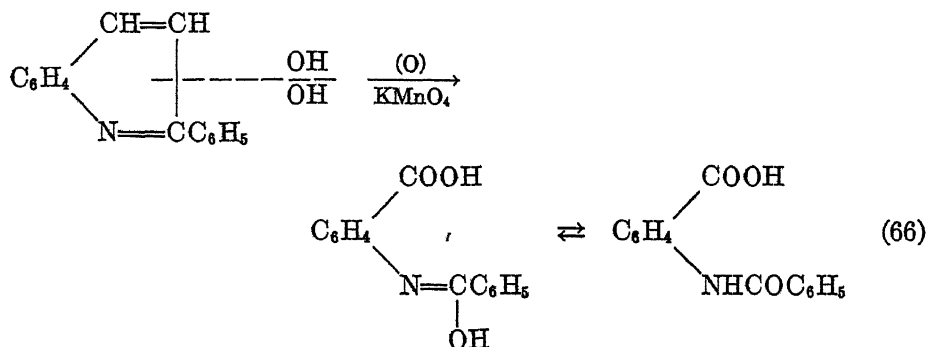
The yield of the acid was 1.5 g. from 5 g. of 2-phenylquinoline. Quinaldine similarly yields N-acetylanthranilic acid, but anthranilic acid and oxalic acid are obtained at the same time (255).

When an aquo ketone is oxidized the bond between the carbonyl and an adjacent group is broken, and a mixture of acids (or of acids and ketones) is formed, as in the following example:

$$RCH_2COCH_2R \rightarrow RCOOH + RCH_2COOH \quad (66a)$$
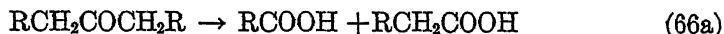
The bond that is ruptured in the case of 2-phenylquinoline is similarly attached to the ammonia analogue of the carbonyl group, that is, to —C=N— (S. Skraup (763) calls this a carbimide group).

When quinoline itself is oxidized with dichromic acid, the pyridine ring is not much affected, since pyridine-2, 3-dicarboxylic acid (quinolinic acid) is formed.

The stability of the pyridine nucleus may well have been increased by the positive charge on the nitrogen of the salt that is present in the acid solution. Quinolinic acid may be prepared in 65 per cent yield by oxidizing quinoline with hydrogen peroxide in the presence of cupric sulfate (779).

(b) Benzoyl chloride and quinoline react in 10 per cent aqueous sodium hydroxide to form o-benzoylaminocinnamaldehyde, as shown by the following equations:

$$
\begin{array}{c}
CH{=}CH \\
C_6H_4 \quad\quad \xrightarrow{C_6H_5COCl} \quad \left[C_6H_4 \quad\quad \right]^+ Cl^- \xrightarrow{OH^-} \\
N{=}CH \\
\quad\quad COC_6H_5
\end{array}
$$

$$
\begin{array}{c}
CH{=}CH \\
C_6H_4 \quad\quad \longrightarrow \quad C_6H_4 \quad CH{=}CHCHO \\
N{-}CHOH \quad\quad NHCOC_6H_5 \\
COC_6H_5
\end{array} \qquad (67)
$$
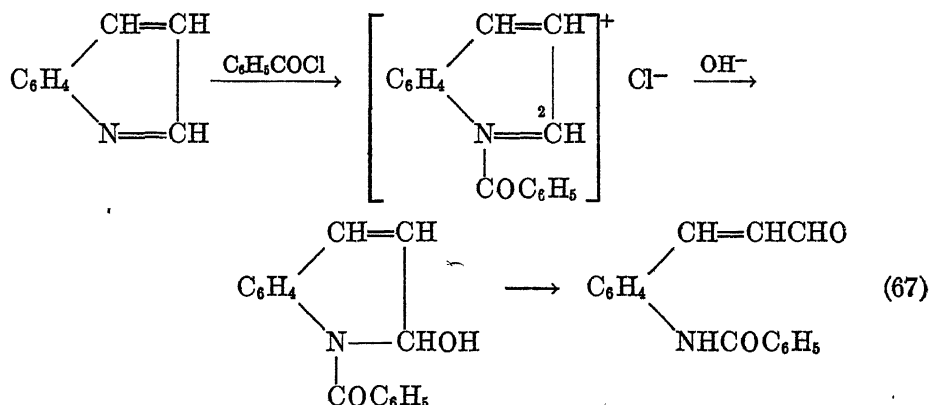
The hydroxyl ion of the sodium hydroxide adds to the carbon atom No. 2 to give 1-benzoyl-2-hydroxy-1, 2-dihydroquinoline, which supposedly exists as the open-chain o-benzoylcinnamaldehyde (706, 707).

(c) A possible ring opening was obseved by Mikhailenko and Minof'ev (605), who treated benzylquinolinium chloride with a number of aromatic and aliphatic amines (p-toluidine, piperidine, aniline, diphenylamine, etc.) and obtained red compounds which probably had one of the structures given below (cf. 509; and Section II, C, (a)):

$$
\begin{array}{c}
CH{=}CH \\
C_6H_4 \\
N{-}CHNHC_6H_4CH_3(p)\cdot HCl \\
CH_2C_6H_5
\end{array}
\qquad\qquad
\begin{array}{c}
CH{=}CHCH{=}NC_6H_4CH_3 \\
C_6H_4 \\
NHCH_2C_6H_5\cdot HCl
\end{array}
$$
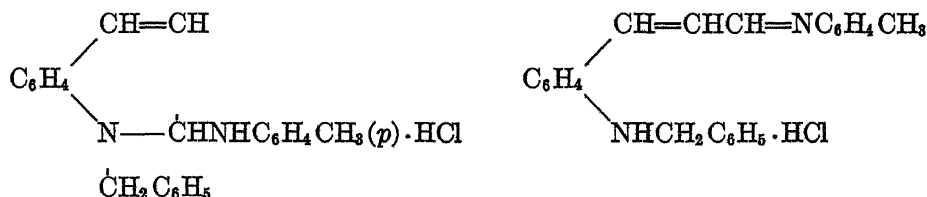
(d) Mumm and Herrendörfer (632) treated quinoline with cyanogen bromide to obtain the addition compound (I) below, which reacts with anhydrous hydrogen cyanide to give a dicyanide (II). Methyl alcoholic ammonia changes this to an isomer, for which the open-chain structure (III) has been suggested.

$$
\begin{array}{c}
CH{=}CH \\
C_6H_4 \quad\quad \xrightarrow{CNBr} \quad \left[C_6H_4 \quad\quad \right]^+ Br^- \xrightarrow{HCN} \\
N{=}CH \\
\quad\quad CN
\end{array}
$$

$$
\begin{array}{ccc}
\underset{C_6H_4}{\overset{\displaystyle CH=CH}{\diagdown\quad\big|}} & & \underset{C_6H_4}{\overset{\displaystyle CHCH=CHCN}{\diagup\quad\diagdown}} \\
\overset{\displaystyle N—CHCN}{\underset{\displaystyle CN}{\big|}} & \begin{array}{c}NH_3 \text{ in}\\ CH_2OH\end{array} & NCN
\end{array}
\tag{68}
$$

$$\text{II} \qquad\qquad\qquad\qquad \text{III}$$
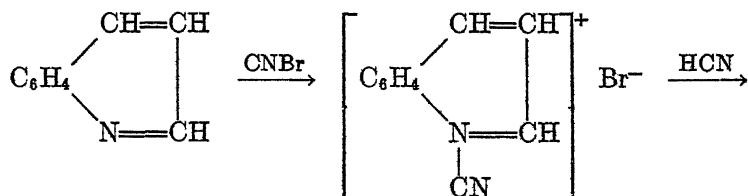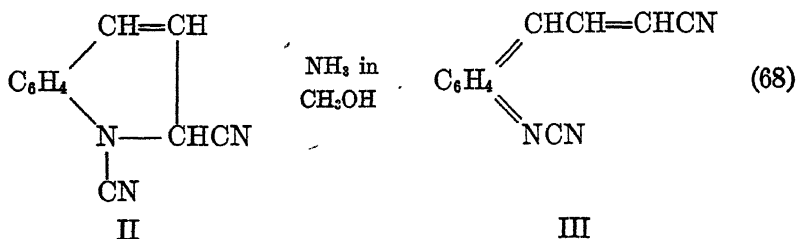
(e) The pseudo bases which are obtained by the action of alkali on the quinaldine alkiodides are so reactive that they have often been assigned open-chain structures, although the bulk of the evidence seems to support the ring formulas.

<center>C. REDUCTION OF QUINOLINE</center>

Quinoline may easily be reduced catalytically or with tin and concentrated hydrochloric acid to 1,2,3,4-tetrahydroquinoline (85, 428, 520a, 652, 652a, 737a, 737b, 762). The reduction to the decahydro stage is somewhat more difficult (32a, 32b, 441, 652a, 762). Ahrens (5) reports that the electrolytic reduction of quinoline in sulfuric acid solution with a lead cathode gives tetrahydroquinoline, together with dimeric and trimeric dihydroquinolines. Electrolysis of quinoline in potassium hydroxide with a platinum anode and mercury cathode in a divided cell (558) gives monomeric and polymeric 1,4-dihydroquinolines. Tetrahydroquinoline (43 per cent) and amorphous dihydroquinoline polymer (38 per cent) are formed by reducing quinoline with sodium in absolute alcohol; poor results are obtained by using ordinary 95 per cent alcohol (32a, 32b).

Addition of 1 mole of hydrogen to quinoline should give either 1,2-dihydroquinoline, the corresponding unsaturated cyclic ammono alcohol, or 1,4-dihydroquinoline. Attempts to prepare either of these have generally given their polymers (cf. 5, 32a, 32b, 558). Knowles and Watt (488) have recently reduced quinoline and some of its derivatives with sodium in liquid ammonia, obtaining, apparently, 1,4-dihydroquinoline, which was isolated as the diacetylated dimer. Attempts to reduce quinaldine to a dihydroquinaldine with hydrochloric acid and zinc dust have given the dimer instead (419).

Dialkyl derivatives of 1,2-dihydroquinoline, however, do exist (Section IV, N, 4). The parent compounds are intermediates in many of the quinoline ring syntheses.

<center>D. BIQUINOLINES (BIQUINOLYLS, DIQUINOLYLS)</center>

2,2′-Diquinolyl,

$$
\underset{C_6H_4}{\overset{\displaystyle CH=CH \quad HC=CH}{\diagup\quad\big|\qquad\big|\quad\diagdown}}_{\displaystyle N=C———C=N}C_6H_4
$$
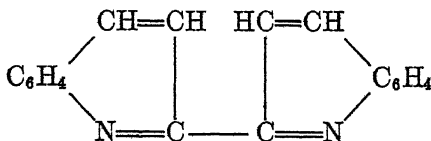
is a cyclic ammono diketone diether, an analogue of benzil, $C_6H_5COCOC_6H_5$. It may be made by the following methods:

(a) By heating quinoline at 325–335° C. with nickel–alumina in a sealed glass tube in 15 per cent yield (814b).

(b) By reducing a mixture of 2- and 7-bromoquinolines with hydrazine hydrochloride in alcoholic potassium hydroxide solution, in the presence of palladium on calcium carbonate (799a); 7,7'- and 2,7'-biquinolyls are also formed.

(c) By a Friedländer synthesis from methyl 2-quinolyl ketone and o-aminobenzaldehyde, or from 2 moles of the latter and 1 mole of diacetyl (767b).

2,3'-Diquinolyl,
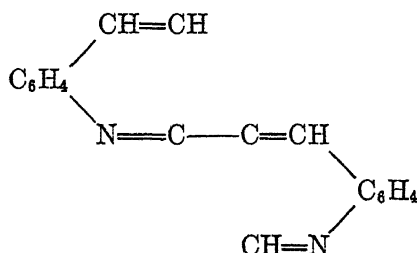
is a cyclic ammono ketone aldehyde diether, analogous to water system compounds of the type CH_3COCH_2CHO or $C_6H_5COCH(C_6H_5)CHO$. The dihydro compound (see equation 79) is to be regarded as formed by the "aldol" condensation of quinoline.

2,3'-Diquinolyl may be prepared:

(a) By the action of sodium on quinoline, in 30–40 per cent yield (807b). Weidel and coworkers (807c) believed that they had obtained 2,2'-diquinolyl, but Einhorn and Sherman (273a) showed it to be the 2,3'-isomer by synthesizing it from o-aminobenzaldehyde and 2-quinolylacetaldehyde.

(b) By heating quinoline with sodium amide in an inert solvent; 2-aminoquinoline is also obtained (Section IV, H, 4). Dihydro-2,3'-diquinolyl is formed; it may readily be oxidized to 2,3'-diquinolyl.

(c) By the action of selenium on quinoline at 280–300°C. (799b). One gram of product was obtained from 10 g. of quinoline and 15 g. of selenium. Mills and Ordish (615a) decarboxylated 2,3'-diquinolylcarboxylic acid, which they prepared from 2-quinolylpyruvic acid ester and o-aminobenzaldehyde by a Friedländer synthesis.

(d) By the action of o-aminobenzaldehyde on methyl 3-quinolyl ketone (519a).

Most of the remaining diquinolyls can be prepared by the Skraup reaction from diaminodiphenyls or by the method of Ueda, which consists in the reduction of bromoquinolines, or a mixture of two bromoquinolines, with hydrazine hydrate or hydrochloride in alcoholic potassium hydroxide solution and in the presence of palladized calcium carbonate (see method (b) under 2,2'-diquinolyl). An example of the Skraup synthesis is the formation of 6,6'-diquinolyl from benzidine

(648b). References to the preparation of some individual diquinolyls are given below:

DIQUINOLYL	REFERENCE	DIQUINOLYL	REFERENCE
2,6'— ·	(806a)	5,5'—	(799a)
2,7'—	(799a)	6,6'—	(648b)
3,3'—	(702b, 799c)	7,7'—	(106b, 799a)
3,4'—	(615a)	8,8'—	(639a)
4,4'—	(170a)	3,7' or 4,7'—	(443a)

All of the diquinolyls listed, with the exception of the 2,2'-and 2,3'-isomers, are cyclic ammono dialdehyde diethers.

E. THE ACTION OF ALKALI BISULFITES ON QUINOLINE

Quinoline reacts with sodium bisulfite and potassium bisulfite to form water-soluble addition compounds, which decompose into their constituents at 60–70°C. in aqueous solution (101). Voroshzov and Kogan (803) warmed quinoline with sulfur dioxide in water and obtained the addition compound $C_9H_7N \cdot SO_2$, which they consider to be identical with the one prepared by Brunck and Gräbe (101). It is not known whether the aldehydic —CH=N—linkage of quinoline is involved in the reaction; it seems certain that this is not the case, however, with some azo dyes derived from 8-hydroxyquinoline, which appear to add sodium bisulfite in the 5,8-positions (803).

The related ammono aldehyde ether, benzalaniline, reacts with aqueous sulfur dioxide to give a compound that is considered to have the formula (269, 479, 776; *cf.* 650):

$$C_6H_5CHNHC_6H_5$$
$$|$$
$$SO_3H \cdot C_6H_5NH_2$$
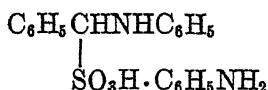
It may be regarded as the aniline salt of a sulfurous acid addition compound of the ammono aldehyde ether.

F. THE ACTION OF BENZOYL CHLORIDE AND ALKALI ON QUINOLINE

Benzoyl chloride (2 moles), quinoline, and potassium cyanide react to give 1-benzoyl-2-cyano-1,2-dihydroquinoline in almost quantitative yield (Reissert's reaction; 455, 705). When treated with hydrochloric acid, quinoline-2-carboxylic acid (quinaldic acid) and benzaldehyde are formed, among other substances. It is better to mix the benzoylcyanodihydroquinoline with phosphorus pentachloride in chloroform, whereupon 2-cyanoquinoline may be obtained in yields as high as 55 to 70 per cent of the theoretical (455). Sugasawa and Tsuda (787) hoped to use Reissert's reaction to prepare aromatic aldehydes, but their expectations were only partly fulfilled. The probable equations follow:

$$C_6H_4 \underset{\diagdown N = =\overset{\cdot}{C}H}{\overset{\diagup CH=CH}{\Big\langle}} + C_6H_5COCl$$

$$C_6H_4 \underset{\overset{\diagdown }{\underset{\overset{|}{C}OC_6H_5}{N==\overset{\cdot}{C}H}}}{\overset{\diagup CH=CH\rceil^+}{\Big\langle}} Cl^- \xrightarrow{K^+CN^-} C_6H_4 \underset{\overset{\diagdown }{\underset{\overset{|}{C}OC_6H_5}{N-\overset{\cdot}{C}HCN}}}{\overset{\diagup CH=CH}{\Big\langle}} + KCl$$

$$\quad\quad\quad\quad\quad\quad I \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad II$$

$$II + PCl_5 \rightarrow C_6H_4 \underset{\diagdown N==CCN}{\overset{\diagup CH=CH}{\Big\langle}}$$

$$III$$

$$+ C_6H_5CHO \text{ (perhaps also } C_6H_5COCl) \quad (69)$$
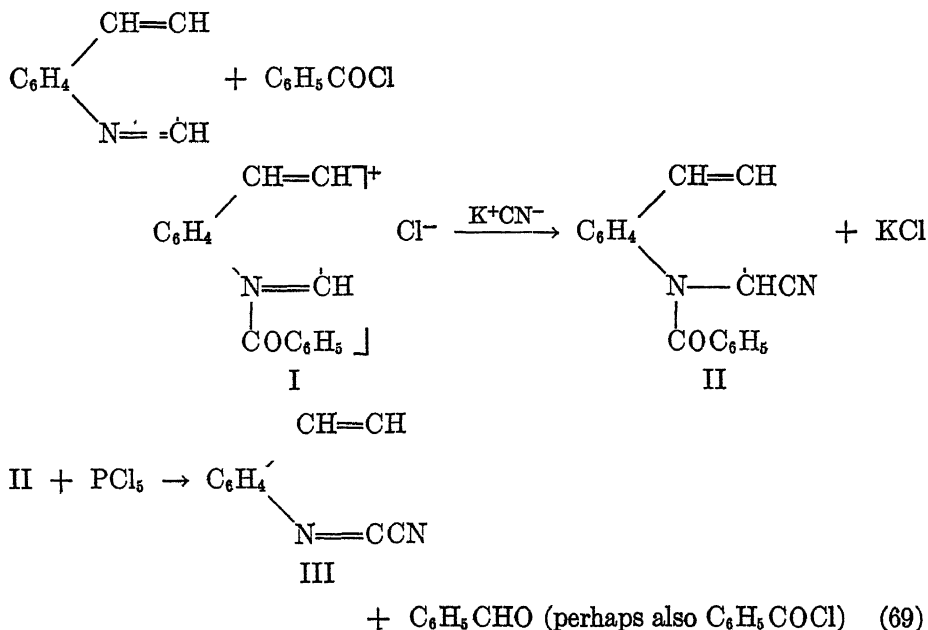
When hydrochloric acid is used in place of the phosphorus pentachloride, the 2-cyanoquinoline is hydrolyzed to quinaldic acid.

The addition compound (I) reacts with cyanide ion to form 1-benzoyl-2-cyano-1,2-dihydroquinoline (II), from which benzaldehyde may be abstracted to give quinaldonitrile (III). The second step of the reaction may be regarded as an indirect addition of hydrocyanic acid to quinoline, an ammono aldehyde ether, to give a cyanohydrin, which is isolated as its benzoyl derivative. There is some analogy in the use of benzoyl chloride to form a quinoline cyanohydrin, and in the use of the bisulfite addition compound of benzaldehyde to form mandelonitrile, or benzaldehyde cyanohydrin. The addition of the cyanide ion to the 2-carbon of quinoline (equation 69) is doubtless accelerated by the positive charge on the cation of I; in fact, it will not occur without this activation.

Benzoyl mandelonitrile, $C_6H_5CH(CN)OCOC_6H_5$, is an approximate water system analogue of II, the benzoyl derivative of the hypothetical quinoline cyanohydrin:

$$C_6H_4 \underset{\underset{H}{\diagdown N---CHCN}}{\overset{\diagup CH=CH}{\Big\langle}}$$
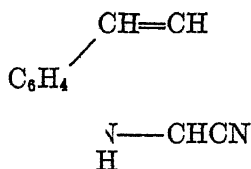
The former may be made, in a manner paralleling equation 69, by allowing benzoyl chloride, benzaldehyde, and potassium cyanide to react (319). It is interesting that the product is not decomposed by prolonged boiling with dilute acids.

G. QUINOLINES HYDROXYLATED IN THE PYRIDINE NUCLEUS

2-Hydroxyquinoline (I) and 4-hydroxyquinoline (III) are tautomeric, respectively, with 2-quinolone (II) and 4-quinolone (IV); it is possible that the isomerism is as complicated as that of the hydroxypyridines (see Section II, K; references 352, 354, 355, 356; cf. 20a).

$$
\begin{array}{ccccc}
\text{CH=CH} & & \text{CH=CH} & \overset{\text{OH}}{\underset{|}{\text{C}}\text{=CH}} & \text{CO—CH} \\
\diagup & & \diagup & \diagup & \\
\text{C}_6\text{H}_4 & \rightleftarrows\ \text{C}_6\text{H}_4 & | & \text{C}_6\text{H}_4 \quad | & \rightleftarrows\ \text{C}_6\text{H}_4 \\
\diagdown & & \diagdown & \diagdown & \diagdown \\
\text{N=\ \cdot COH} & & \text{NH—CO} & \text{N=CH} & \text{NH—CH} \\
& & \text{II} & \text{III} & \text{IV}
\end{array}
$$
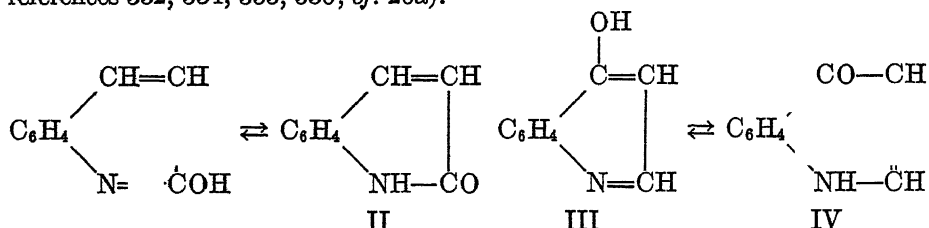
2-Hydroxyquinoline (carbostyryl) in either of its tautomeric forms is a cyclic ammono aquo acid ester, while 4-hydroxyquinoline is its vinylogue. In neither of these is the hydroxyl group as phenolic as it is in 3-hydroxyquinoline.

2-Hydroxyquinoline may be prepared by the following methods: (a) Oxidation of quinoline by means of bleaching powder solution at 100°C. (2–3 hr.) (275, 284, 716, 795). In this reaction, a cyclic ammono aldehyde ether has been oxidized to the corresponding cyclic ammono aquo acid ester.

(b) Ring-closure reactions, such as the two already mentioned (Section IV, A, 7–8), and the following:

(1) o-Nitrocinnamic acid or its esters when reduced give carbostyryl (27, 288, 353, 695, 791). The assumed intermediate, o-aminocinnamic acid, is by itself changed only slowly to carbostyryl; its acetyl derivative is changed readily (27).

$$
\begin{array}{c}
\text{CH=CHCOOH} \\
\diagup \\
\text{C}_6\text{H}_4 \qquad\qquad \xrightarrow{\text{(6H)}} \\
\diagdown \\
\text{NO}_2
\end{array}
\qquad
\begin{array}{c}
\text{CH=CH} \\
\diagup \\
\text{C}_6\text{H}_4 \qquad | \\
\diagdown \\
\text{N==COH}
\end{array}
\ +\ 3\text{H}_2\text{O} \qquad (70)
$$
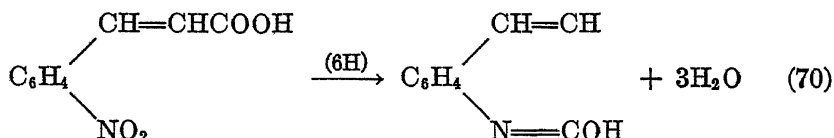
Carbostyryl can therefore be regarded as formed by the intramolecular esterification of the aquo acid-ammono phenol, o-aminocinnamic acid,

$$
\begin{array}{c}
\text{CH=CHCOOH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{NH}_2
\end{array}
$$
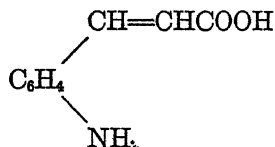
and the correctness of its assumed relationship to the ammonia system is shown.

(2) o-Acetaminobenzaldehyde, when boiled with aqueous alcoholic potassium hydroxide, gives carbostyryl in 80 per cent yield (107).

$$
\begin{array}{c}
\text{CHO} \\
\diagup \\
\text{C}_6\text{H}_4 \qquad\qquad \xrightarrow[\text{heat}]{\text{NaOH}} \\
\diagdown \\
\text{NHCOCH}_3
\end{array}
\qquad
\begin{array}{c}
\text{CH=CH} \\
\diagup \\
\text{C}_6\text{H}_4 \qquad | \\
\diagdown \\
\text{N==COH}
\end{array}
\ +\ \text{H}_2\text{O} \qquad (71)
$$
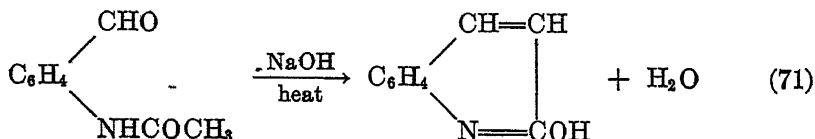
It will be noted that the —$C_6H_4NHCOCH_3$ portion of the molecule represents a monosubstituted acetamide and therefore an ammono aquo acid ester, as acetamide is an ammono aquo acid. The ring closure is merely a Claisen reaction between the ortho —CHO and an active methyl group, which is analogous to the methyl group in an ester of acetic acid, CH_3COOR.

(3) 2-Chloroquinoline—a cyclic ammono acid chloride ester (Section IV)—is hydrolyzed to carbostyryl when heated to 120°C. with water containing a little hydrochloric acid (764; *cf.* 179). 4-Hydroxyquinoline is similarly prepared from 4-chloroquinoline (76).

(4) Chichibabin (114, 131, 143a) prepared carbostyryl in yields of 80 per cent and better by heating quinoline with dry potassium hydroxide or barium hydroxide for a few hours at about 225°C. Small quantities of indole may be formed in the reaction, but this is not unexpected, since indole may be made, along with other compounds, by melting carbostyryl with potassium hydroxide (628). The reaction of Chichibabin follows the equation:

$$C_6H_4 \underset{N=\!=\!CH}{\overset{CH=\!CH}{<}} + KOH = C_6H_4 \overset{CH=\!CH}{\underset{N=\!=\!COK}{<}} + H_2 \quad (72)$$
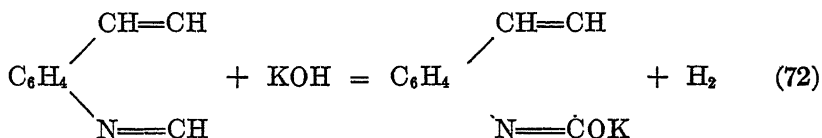
Carbostyryl itself is obtained by acidifying an aqueous solution of its potassium salt. Many substituted quinolines react similarly (114, 143a, 243).

Properties of carbostyryl: When carbostyryl is oxidized with cold potassium permanganate, isatinic acid,

$$C_6H_4 \underset{NH_2\text{-}o}{\overset{COCOOH}{<}}$$
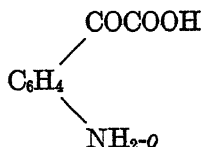
(→ isatin) is formed by ring scission and loss of one atom of carbon; at the same time, oxalylanthranilic acid is obtained, by the oxidation of the double bond in the 3,4-position (349).

$$C_6H_4 \underset{NH-CO}{\overset{CH=\!CH}{<}} \quad \overset{KMnO_4}{\longrightarrow} \quad C_6H_4 \underset{NHCOCOOH}{\overset{COOH}{<}} \quad (73)$$
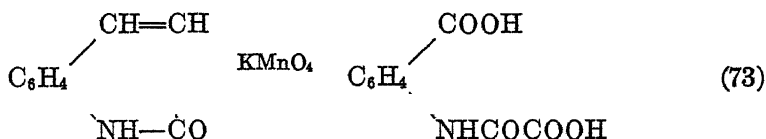
Cinnamic acid is similarly oxidized by dilute dichromic acid or by alkaline boiling permanganate to benzaldehyde (603, 761). Crotonic acid, $CH_3CH=\!CHCOOH$, is oxidized by concentrated nitric acid to acetic and oxalic acids, or by chromic acid mixture to acetaldehyde and acetic acid (470).

Arndt, Eistert, and Ender (15) have concluded that the 3-hydroxyl group is more acidic than the 2-hydroxyl, as the result of an experiment in which they methylated isatin with diazomethane and obtained 2,3-dihydroxyquinoline, together with 2-hydroxy-3-methoxyquinoline.

H. 2-, 3-, AND 4-HALOGENATED QUINOLINES

2-Chloroquinoline, a cyclic ammono acid chloride ester, is made, as are the aquo acid chlorides, by the action of phosphorus pentachloride and phosphorus oxychloride on 2-hydroxyquinoline, but at the higher temperature of 130–140°C. (350). It may also be made by treating N-methyl-α-quinolone, a cyclic ammono aquo ester, with the same mixture of reagents (293, 304) or with phosgene (698). 2-Bromoquinoline is similarly prepared (167, 299, 304, 778). Quinoline may be brominated in the gaseous phase over a pumice catalyst at 300°C. to give a 25 per cent yield of 3-bromoquinoline (442b; $cf.$ 163a), and at 450°C. to give a 24 per cent yield of 2-bromoquinoline (442b). The yield of the latter may be increased to 53 per cent by passing the quinoline and bromine through an empty tube at 500°C., with a carrier of nitrogen gas. 4-Chloroquinoline is prepared, along with some 2-chloroquinoline, by the action of sulfuryl chloride on quinoline N-oxide (77, 591a) and, free from isomers, by heating 4-hydroxyquinoline (kynurine) with phosphorus halides (23a, 542, 764) or with benzoyl chloride (277), or by diazotizing 4-aminoquinoline in concentrated hydrochloric acid solution (165, 810). 4-Bromoquinoline may be made either from kynurine or from 4-aminoquinoline (166a). Treatment of 3-acetoxymercuriquinoline with potassium bromide gives 3-bromoquinoline (799e).

Of the 2-, 3-, and 4-halogenoquinolines, the 2- and 4-isomers are the most reactive, though much less so than a typical open-chain acid chloride of the water system. The fused benzene ring of quinoline seems to be responsible for increasing the mobility of a 2- or 4-substituted chlorine over that of the 2- and 4-chloropyridines (296). A number of examples follow.

1. Preparation of alkoxyquinolines

2-Chloroquinoline is readily converted to 2-methoxyquinoline (a cyclic ammono aquo ester) by short heating with sodium methylate in methanol, or into 2-ethoxyquinoline by heating with ethyl alcoholic potassium hydroxide (78, 351). In one case, at least, partial isomerization has been reported, since Bogert and May (78) find that a mixture of 80 per cent of 2-isoamyloxyquinoline and 20 per cent of 1-isoamyl-2-quinolone is formed by heating 2-chloroquinoline with sodium isoamylate. 4-Chloroquinoline may similarly be converted to 4-alkoxyquinolines (811).

A phenyl group in the 2-position does not appear greatly to influence the reactivity of a 4-chlorine atom, since it is necessary to heat 2-phenyl-4-chloroquinoline with alcoholic potassium hydroxide for 8 hr. at 145–165°C. to prepare 2-phenyl-4-ethoxyquinoline (444b).

2. Preparation of phenoxyquinolines

2-Phenoxyquinoline is made by heating 2-chloroquinoline with sodium phenoxide dissolved in phenol (351). Backeberg and Marais (26) found that the chief product of the action of ammonia gas on a heated phenol solution of 2-chloro-4-methylquinoline was 2-phenoxy-4-methylquinoline. The latter can be prepared somewhat more conveniently by heating the reactants for about 5 hr. at 180°C.,

with omission of the ammonia.   2-Phenyl-4-phenoxyquinoline is formed, apparently with some difficulty, by heating 2-phenyl-4-chloroquinoline with potassium phenoxide in phenol for 10 hr. at 180°C. (444c).   Turner and coworkers have prepared a number of 2- and 4-phenoxyquinolines in connection with the synthesis of compounds of possible therapeutic value (565a, 637).

3. Preparation of thiolquinolines and arylquinolyl sulfones   ·

2-Chloroquinoline is converted to 2-thiolquinoline (III) or 2-mercaptoquinoline (a cyclic thio ammono acid ester) by heating with potassium hydrosulfide in alcohol for a few hours at 150°C. (300).   2-Phenylquinoline-4-thiol is similarly formed from 4-chloro-2-phenylquinoline but seemingly less readily (444a).   It is better to heat 2-chloroquinolines with thiourea on the water bath for about 15 min., whereupon the following series of reactions occur (721):

$$\text{II} + \text{NH}_3 \text{ or } \text{Na}_2\text{CO}_3 \text{ or heat} = \text{C}_6\text{H}_4 \overset{\text{CH}_3}{\underset{\text{N}=\text{CSH}}{\overset{\text{C}=\text{CH}}{|}}} + \text{CNNH}_2$$
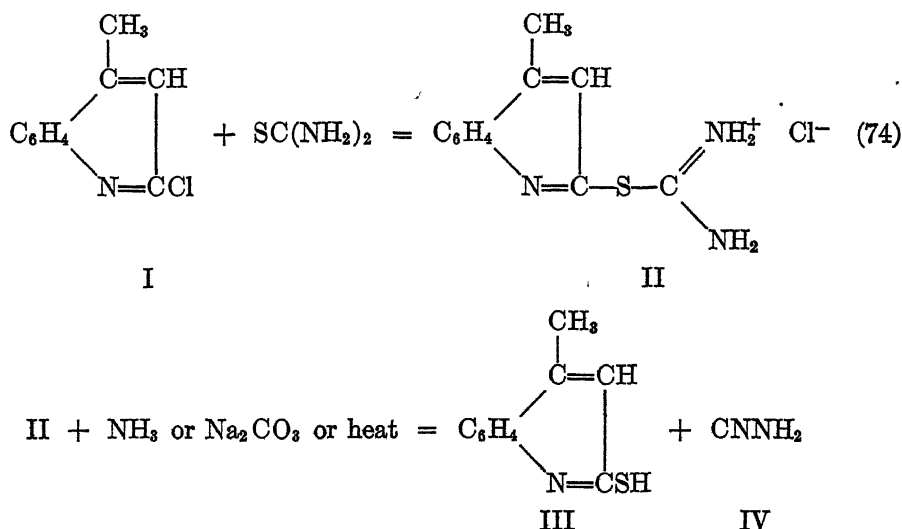
An addition compound of the possible structure II is first formed, but this can be isolated only by working in the cold.   When treated with ammonia or sodium carbonate or heated, a thiolquinoline (III) is obtained, together with cyanamide (IV) or its polymerization product, dicyanodiamide.   Thiourea is a thioammonocarbonic acid, while cyanamide and dicyanodiamide are ammonocarbonic acids.   Under the above conditions, 4-chloroquinaldine is largely converted to (2,2'-dimethyldiquinolyl-4,4') sulfide.

Aryl quinolyl sulfones, $C_9H_6NSO_2Ar$, may be made by heating 2-chloroquinoline with sodium aryl sulfinates for several days at 100°C. (794).

4. Preparation of amino- and substituted amino-quinolines

2-Aminoquinoline and 2-hydroxyquinoline are formed when 2-chloroquinoline is heated with aqueous ammonia and ammonium carbonate at 200–210°C. (168). 2-Aminoquinoline may be prepared in 50 per cent yield by heating 2-bromoquinoline with liquid ammonia in the presence of copper powder (6 hr. at 70°C.

(443)). (For the preparation of substituted 2-aminoquinolines, see reference 318.) 3-Aminoquinoline is made by the ammonolysis of 3-bromoquinoline in liquid ammonia, with added copper powder, or in aqueous ammonia with copper sulfate as a catalyst (711). Halogen in position 3 is less reactive than in position 2 or 4.

2-Chloroquinoline (or 4-chloroquinaldine) and aniline react at about 200°C. to give 2-anilinoquinoline (23, 24, 357). Backeberg and Marais (26) have obtained 4-amino-2-methylquinolines in almost quantitative yield by passing ammonia into a hot phenol solution of the corresponding 4-chloro-2-methylquinoline (2 hr. at 180°C.), but the 2-chloro-4-methylquinolines give only small yields (about 10 per cent) of amines, the main product being a 2-phenoxy-4-methylquinoline. To prepare the 2-amino-4-alkylquinolines, it is best to heat the 2-chloro-4-alkylquinolines with ammoniated zinc chloride in a sealed tube.

Substituted 4-chloroquinolines react with arylamines at elevated temperatures to give 4-arylaminoquinolines (23, 283, 595).

Bobranski (75a) and Gray (379a) heated sulfanilamide with 2-chloroquinoline and obtained 4-(2'-quinolylamino)benzenesulfonamide (I), while Phillips (686a) prepared the isomeric 2'-(4-aminobenzenesulfonamido)quinoline (II) by carrying out the reaction in the presence of potassium carbonate and a trace of copper (cf. Section II, M, 4).

$$CH=CH$$
$$C_6H_4$$
$$N=CNHC_6H_4SO_2NH_2\text{-}4$$
I

$$CH=CH$$
$$C_6H_4$$
$$N=CNHSO_2C_6H_4NH_2\text{-}4$$
II
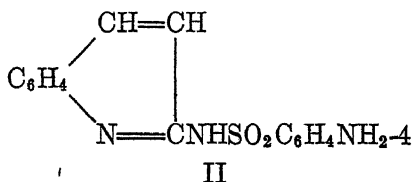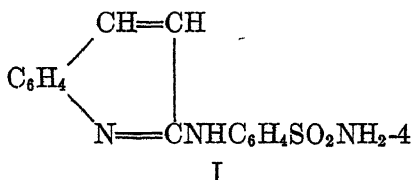
5. Preparation of hydrazino- and phenylhydrazino-quinolines

2-Hydrazinoquinoline is best made by refluxing 2-chloroquinoline with hydrazine hydrate for 1 hr. (684a). If carried out in sealed tubes at higher temperatures, this reaction is not only less convenient, but also gives some sym-di-2-quinolylhydrazine, Qu·NHNH·Qu (587a). 2-Hydrazino-4-methylquinoline and 4-hydrazino-2-methylquinoline have been prepared by heating the corresponding chlorine compound with hydrazine hydrate for 5 hr. at 150°C. (585a; see reference 501 for structure).

Koenigs and von Loesch (501; cf. 102a) report that two products are formed by the action of hydrazine hydrate on 4-chloroquinaldine: one was the expected 4-hydrazinoquinaldine, while the other was a diaminoquinaldine of unknown structure.

2-Phenylhydrazinoquinoline (281a) and 2-phenylhydrazino-4-methylquinoline (281b) are easily made by heating the respective chloroquinolines with phenylhydrazine. Backeberg (25) finds that phenylhydrazine reacts with derivatives of 4-chloroquinoline to give two isomeric products under slightly different experimental conditions. At 200°C., in an inert solvent, there is formed the ex-

pected 4-phenylhydrazinoquinoline, while at 200°C. in a sealed tube there is obtained an isomer, which is considered to be a 3-anilino-4-aminoquinoline. Ephraim (282) has prepared 4-phenylhydrazinoquinaldine by heating 4-chloro-quinaldine and phenylhydrazine at 115°C.

The hydrazino- and phenylhydrazino-quinolines may in general be reduced to the corresponding aminoquinolines by zinc dust and acid, or by hydrogen iodide and red phosphorus (281, 501b, 587).

6. Preparation of hydroxyquinolines

The replacement of a 2- or 4-chlorine by hydroxyl has in general been fully covered elsewhere (Section IV, G, 3; IV, H, 7). Some carbostyryl is obtained when 2-chloroquinoline is heated with ammonium carbonate and aqueous ammonia at 200°C. (168), or with aqueous alcoholic potassium cyanide at 200°C. (443).

7. Reactivity of 2- and 4-halogen as influenced by other groups

There seems to be little definite evidence concerning the relative reactivities of chlorine in the 2- and 4-positions. Buchmann and Hamilton (104) refluxed 2,4-dichloroquinoline with a solution of potassium hydroxide in methanol and obtained a mixture of 2-chloro-4-ethoxyquinoline (31 per cent), 4-chloro-2-ethoxy-quinoline (32 per cent), and 4-chloro-2-hydroxyquinoline (5.5 per cent). These results might be interpreted as indicating a slightly greater reactivity of a 2-chlorine, in accordance with expectation because of greater proximity to the —C=N— group.

There is, however, a very marked difference in the reactivity of chlorine provided a hydroxyl group is present in the same ring. Thus, Friedländer and Müller (348) state that 4-chloro-2-hydroxyquinoline does not react with boiling sodium alkoxide solutions, and gives 2,4-dihydroxyquinoline only when melted with alkalies. Ephraim (283) finds that while aniline and 4-chloroquinoline react at 120°C. to give 4-anilinoquinoline, the halogen in 4-chloro-2-hydroxyquinoline cannot be similarly replaced. On the other hand, 2,4-dichloroquinoline is converted to 2,4-dianilinoquinoline when heated with aniline, and 2-ethoxy-4-anilinoquinoline may similarly be prepared from 2-ethoxy-4-chloroquinoline. According to Buchmann and Hamilton (104), the halogen in 4-chloro-2-hydroxy-quinoline is quite inactive, while the chlorine in 2-chloro-4-hydroxyquinoline and both halogens in 2,4-dichloroquinoline are active. The halogen in 2-chloro-4-ethoxyquinoline is fairly active, while that in 4-chloro-2-ethoxyquinoline is much more inert. Therefore, hydroxyl in the 2-position will make a 4-chlorine atom much more inert, and groups of the type of ethoxyl or phenylamino (C_6H_5NH—) will have less influence, wherever they may be. A possible explanation, based on interference with the normal activation of the chlorine, is given below.

When either of the hydroxychloroquinolines reacts with a basic reagent, such as sodium ethoxide, the ions shown below will be formed:

$$O^-$$
$$|$$
$$C=CH$$

$$C_6H_4$$

$$N=\overset{\cdot}{C}Cl$$

$$Cl$$
$$|$$
$$C=CH$$

$$C_6H_4$$

$$N=C-O^-$$

II
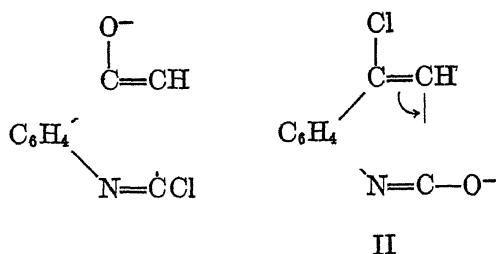
According to recent electronic theories, replacement of chlorine by ethoxyl or a similar group is preceded by an activation in the sense of the arrows in I and II, which places a (temporary) positive charge on the 2- or 4-carbon atom, respectively. These changes, if completed, will give the (unperturbed) forms, III and IV.

$$O^-$$
$$|$$
$$C=CH$$

$$C_6H_4$$

$$N-C-Cl$$
$$- \quad +$$

III

$$Cl$$
$$|$$
$$C^+-CH$$

$$C_6H_4$$

$$N-C-O^-$$
$$-$$

IV
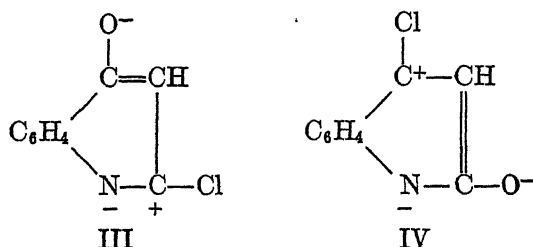
An ethoxyl, $C_2H_5O^-$, or related ion unites with the positively charged carbon of III or IV, and this is followed by elimination of chlorine.

The activation of the 4-carbon atom in IV will be greatly hindered by a resonance involving the negatively charged oxygen, in the manner shown below:

$$Cl$$
$$|$$
$$C=CH$$

$$C_6H_4$$

$$N=C-O^-$$

II

$$\longleftrightarrow$$

$$Cl$$
$$|$$
$$C=CH$$

$$C_6H_4$$

$$N-C=O$$
$$-$$

V
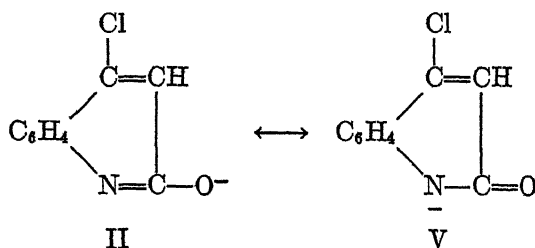
Essentially, of course, this is the 2-hydroxyquinoline–2-quinolone tautomerism. The related resonance, giving the unperturbed form,

$$O$$
$$\|$$
$$C-CH$$

$$C_6H_4$$

$$N-C-Cl$$
$$-$$

VI
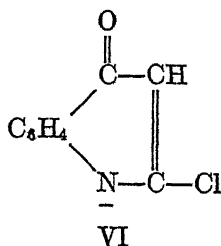
apparently will not prevent the activation of the 2-chlorine, as in III, though there may well be some hindrance. With an alkoxy or phenylamino group in the 2- or 4-position, resonance of the type shown below will be of less importance, and will accordingly not influence the reactivity of a 2- or 4-halogen as much as will a hydroxyl group.

$$-N{=}\overset{|}{C}-OR \longleftrightarrow -\underset{-}{N}-\overset{|}{C}{=}\overset{+}{O}R$$
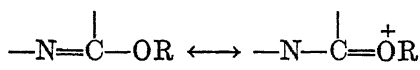
4-Chloro-1-methyl-2-quinolone (VII) reacts with alcoholic metal alkoxides on short heating to give 4-alkoxy derivatives, in accordance with the following equation (348):

$$(74a)$$
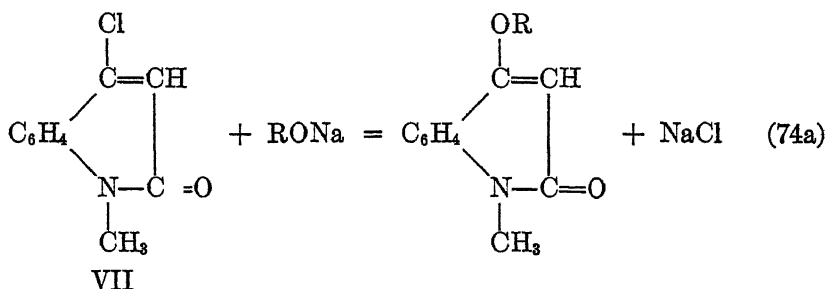
The effect of the carbonyl upon the mobility of the chlorine has therefore been damped but little in transmission across the conjugated system,

$$O{=}\overset{|}{C}-CH{=}\overset{|}{C}-Cl$$
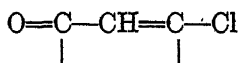
partly because ring resonance does not interfere as much where there are only two cyclic double bonds.

I. ALKOXYQUINOLINES, N-ALKYLQUINOLONES

It has been previously shown that these compounds are cyclic ammono aquo esters (Section I, G); their preparation has been adequately discussed elsewhere (Section IV, H, 1, Section IV, N, 2, (c) and (d)).

2- or 4-Alkoxyquinolines may generally also be made by heating the silver salts of the corresponding hydroxyquinolines (carbostyryl or kynurine, respectively) with an alkyl halide (346a, 356; cf. 811a). Alkylation of carbostyryl or kynurine with alkyl halides and alkali usually gives a preponderating amount of the isomeric N-alkylquinolone (346a, 353, 356; cf. 811a), though Meyer (598, 601) reports that 2-methoxyquinoline is formed by methylating carbostyryl with dimethyl sulfate (no experimental details are given).

Diazomethane in ethereal solution converts both 2- and 4-hydroxyquinolines into their O-methyl ethers (=alkoxyquinolines) (598, 599b). 2-Ethoxyquinoline has also been made by cyclizing ethyl 2-aminocinnamate with concentrated zinc chloride in alcohol at 80–90°C. (355).

The reactivity of an alkoxy group in the 2- or 4-position of the quinoline nu-

cleus is somewhat more than that of the same group in an ordinary ether, though less than that of the group in an open-chain ester. A few examples follow:

(1) 2-Ethoxyquinoline (I), when heated with methyl iodide for 2 days at 100° C., gives 1-methyl-2-quinolone (II) in good yield (487). Perhaps there is formed first a methiodide of the ethoxyquinoline, which loses ethyl iodide to give II.

$$+ \text{CH}_3\text{I} \longrightarrow \qquad\qquad + \text{C}_2\text{H}_5\text{I} \quad (74b)$$
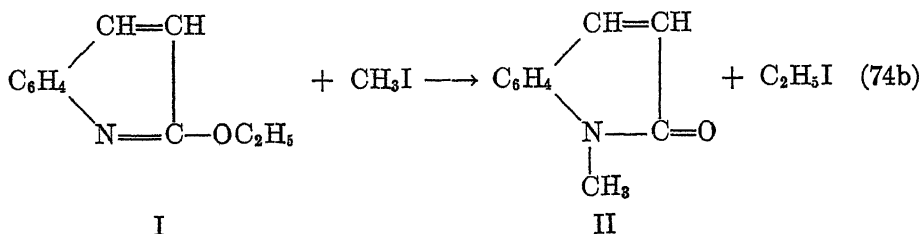
Whatever the mechanism may be, comparison may be made with a *trans*-esterification, or interchange of the alkyl groups attached to the oxygen of an ester. The analogy is not quite exact, since the reaction of equation 74b involves also a rearrangement. The same type of isomerization will take place on simple heating, since the 2-alkoxyquinolines rearrange to the 1-alkyl-2-quinolones (601) at 100°C. and the 4-alkoxyquinolines similarly rearrange to the 1-alkyl-4-quinolones at temperatures in the neighborhood of 280–290°C. (484).

A clearer cut example of a *trans*-esterification has recently been reported by Berinzaghi and coworkers (66). Under the influence of alcoholic alkali, a methoxyl group in the 4-position (with relation to nitrogen) of the alkaloid skimmianine (III) is replaced by the alkoxyl group of the particular alcohol used. The reaction is expressed by the equation:

$$+ \text{ROH} \xrightarrow{\text{NaOR}} \text{CH}_3\text{OH} + \qquad\qquad (75)$$
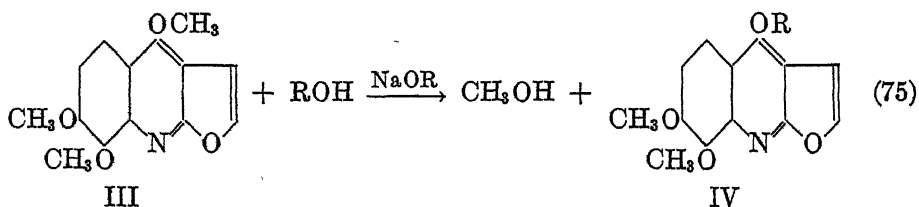
The change is interpreted as involving, first, a 1, 4-addition of the alcohol to the pyridine nucleus, followed by a loss of methanol. The authors correctly consider 4-methoxyquinoline as a vinylogue of an "imino ether", RC(=NH)OR', an ammono aquo acid ester. It will be seen later that related *trans*-esterifications are known in the quinazoline series.

(2) 2-Ethoxyquinoline is stable towards boiling dilute potassium hydroxide (351, 353a, 457), though it is converted to ethyl chloride and 2-hydroxyquinoline when heated with dilute hydrochloric acid at 120°C.; the latter may be slowly formed even at room temperatures (351, 353a, 457). The behavior of an acetal is very similar, since it may be hydrolyzed readily by acids but is comparatively unaffected by alkalies.

(3) Buchmann and Hamilton (104) found that there is a considerable differ-

ence in the ease of replacement of the alkoxyl groups of 2-chloro-4-ethoxyquino-line and 4-chloro-2-ethoxyquinoline by hydroxyl. Thus, the 4-chloro isomer required only 20–30 min. of reflux with 6 N hydrochloric acid, while the 2-chloro compound had to be boiled for 10 hr. with 70 per cent hydrogen iodide before the alkoxyl was replaced by hydroxyl. Furthermore, the yield in the former case was almost quantitative, in the latter about 40 per cent, as calculated from the equation:

$$
\begin{array}{c}
\text{Cl} \\
|\\
\text{C=CH} \\
\diagup\quad\quad| \\
\text{C}_6\text{H}_4\quad\quad\quad + \text{H}_2\text{O} = \\
\diagdown\quad\quad| \\
\text{N=C—OC}_2\text{H}_5 \\
\text{(or isomer)}
\end{array}
\quad
\begin{array}{c}
\text{Cl} \\
|\\
\text{C=CH} \\
\diagup\quad\quad| \\
\text{C}_6\text{H}_4\quad\quad\quad + \text{C}_2\text{H}_5\text{OH}\quad(76) \\
\diagdown\quad\quad| \\
\text{N=C—OH} \\
\text{(or isomer)}
\end{array}
$$
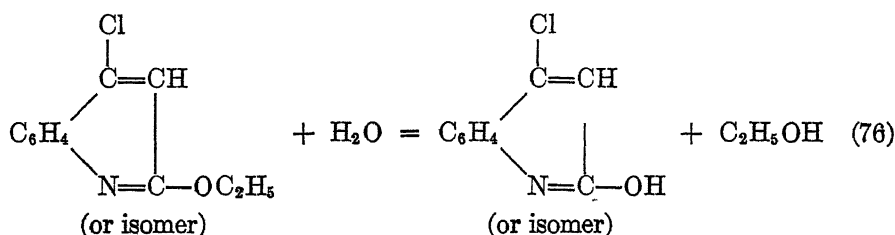
It is interesting that in both cases the alkoxyl group is replaced rather than the chlorine. As expected, the alkoxyl in the 4-position is the less reactive.

(4) 2-Methoxyquinoline readily reacts with potassium amide in liquid ammonia solution to form the potassium salt of 2-aminoquinoline in 51 per cent yield, in accordance with the equation:

$$
\begin{array}{c}
\text{CH=CH} \\
\diagup\quad\quad| \\
\text{C}_6\text{H}_4\quad\quad\quad + 2\text{KNH}_2 = \\
\diagdown\quad\quad| \\
\text{N=C—OCH}_3
\end{array}
\quad
\begin{array}{c}
\text{CH=CH} \\
\diagup\quad\quad| \\
\text{C}_6\text{H}_4\quad\quad\quad \\
\diagdown\quad\quad| \\
\text{N=C—NHK}
\end{array}
$$
$$+ \text{CH}_3\text{OK} + \text{NH}_3 \quad(77)$$
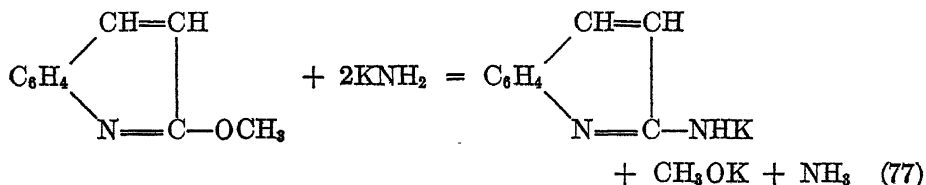
A cyclic ammono aquo ester has been saponified by the strong base, potassium amide, to the potassium salt of a cyclic ammono aquo acid ester, 2-aminoquino-line (58).

The 4-alkoxyquinolines, when heated with ammonium salts either alone or in the presence of ammonia or of alkylamines, give 4-amino- or 4-alkylamino-quinolines (670).

Many 2-alkoxyquinoline-4-carboxylic acids have a local anesthetic activity that is supposed to be due in part to the alkoxyl groups (819).

The 1-alkyl-2-quinolones seem to be less reactive than the isomeric 2-alkoxy-quinolines, as one might expect because ester-like reactions would generally involve a rupture of the ring. The ketonic reactivity of the carbonyl group is low (cf. 347).

J. QUINOLINE-2-SULFONIC ACID

The sodium salts of quinoline 2-sulfonic acid and related compounds are made by heating 2-chloroquinolines with sodium sulfite solution (67). The sulfonic acid group is attached to the same carbon as is the doubly bonded nitrogen, and so is mobile, presumably for that reason. When heated with aqueous ammonia in the presence of zinc chloride at 135°C., 2-aminoquinoline is formed (667), while

with alkylamines it is possible to prepare compounds of the type of 2-dimethyl-aminoquinoline (667).

Quinoline-2-sulfonic acid reacts readily with potassium amide in liquid ammonia at room temperatures to give the potassium salt of 2-aminoquinoline in 74 per cent yield, together with potassium sulfite (59).

A water system analogue of quinoline-2-sulfonic acid will have the formula $C_6H_5COSO_2OH$, but it apparently does not exist. Its reduction product, benzaldehyde sodium bisulfite, $C_6H_5CH(OH)SO_2ONa$, has an easily replaceable sulfonic acid salt group, since mandelonitrile, $C_6H_5CH(OH)CN$, is obtained from it without trouble by the action of sodium cyanide.

K. 2-, 3-, AND 4-AMINOQUINOLINES

2-Aminoquinoline was prepared by Chichibabin and Zatzepina (160) by heating quinoline and sodium amide in the presence of an inert hydrocarbon. The yield is rather low (about 25 per cent), since there is formed at the same time some 2,3-diquinoline (I), which readily reacts with the oxygen of the air to form 2,3-diquinolyl (II). The reactions are expressed by the following equations:

$$\text{(78)}$$

$$\text{(79)}$$
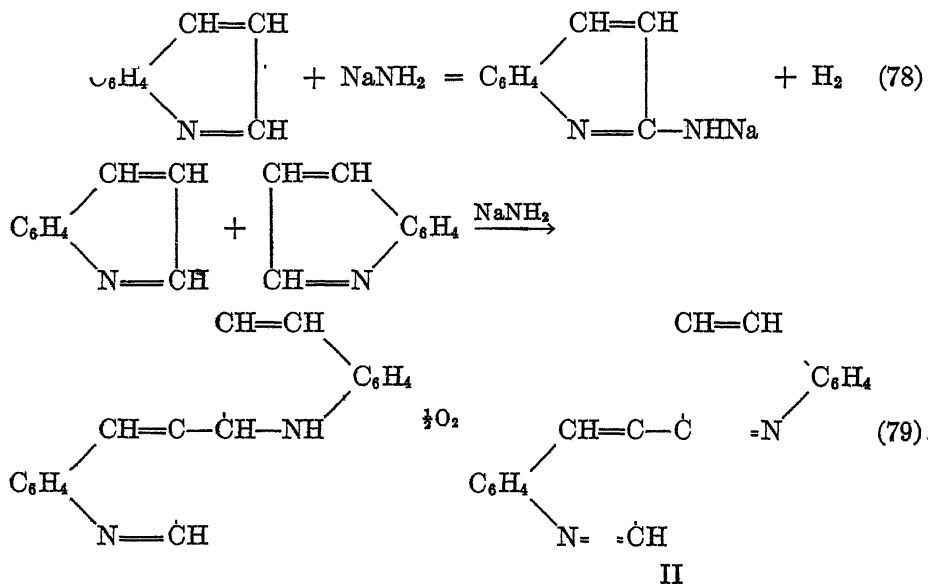
The diquinoline (I) is doubtless present as a sodium salt.

Equation 78 represents the nitridation of quinoline to a salt of a cyclic ammono acid ester, while equation 79 is in its first phase similar to an aldol condensation, since I is a somewhat complex ammonia analogue of aldol (III).

III
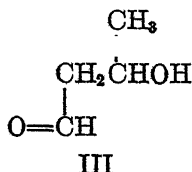
Better yields of 2-aminoquinoline (up to about 80 per cent) are obtained by treating a solution of quinoline in liquid ammonia at room temperatures with barium amide; hydrogen is also formed, much in the manner of equation 78. The reaction is markedly catalyzed by soluble barium salts (52, 55). Quinoline reacts with an excess of potassium amide in liquid ammonia to give resins and oils of indefinite characteristics, but in the presence of potassium nitrate or of mercury there is formed a mixture of 2-aminoquinoline (50–55 per cent) and 4-aminoquinoline (about 10 per cent). The equations are the following (55):

$$C_9H_7N + 2KNH_2 + KNO_3 \rightarrow C_9H_6N—NHK + KNO_2 + KOH + NH_3 \quad (80)$$

$$C_9H_7N + 3KNH_2 + xHg \rightarrow K_2Hg_x + 2NH_3 + C_9H_6N—NHK \quad (81)$$
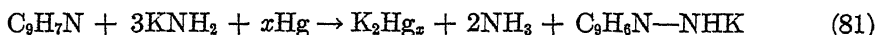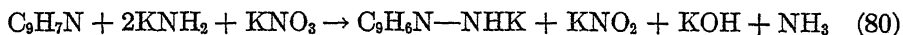
4-Amino-2-phenylquinoline may be obtained in yields as high as 99 per cent of the theoretical by treating 2-phenylquinoline with potassium amide and potassium nitrate in liquid ammonia, in the manner of equation 80 (59a). Here it will be noticed that the 4-hydrogen has the function of the 2-hydrogen of quinoline. Several related liquid ammonia reactions have been described (57). 2-Aminoquinoline may also be made by the ammonolysis of 2-chloroquinoline (Section IV, H, 4), by the action of potassium amide on 2-methoxyquinoline or quinoline-2-sulfonic acid (Sections IV, I, 4; IV, J), and by the reduction of *sym*-di(2-quinolyl)hydrazine (587) or 2-phenylhydrazinoquinoline (281), as well as by other methods.

3-Aminoquinoline may be prepared by the ammonolysis of 3-bromoquinoline (Section IV, H, 4) or of 3-hydroxyquinoline (666a).

2-Cyclohexylaminoquinoline, a cyclic ammono acid ester, is made in 60 per cent yield by heating quinoline with the eutectic of sodium amide and potassium amide (541) in cyclohexylamine (786, 793); the mechanism of the reaction has been discussed previously (Section II, G). 2-Methylaminoquinoline is obtained by treating quinoline with a liquid methylamine solution of sodium methylamide (CH₃NHNa), potassium methylamide, and potassium nitrate, in a manner similar to that of equation 80 (789). Attempts to form mono- and di-methyl-aminoquinolines by heating 2- and 4-aminoquinolines with methyl iodide have given instead the isomeric *N*-methylquinoloneimides, of the type (113b) shown below:
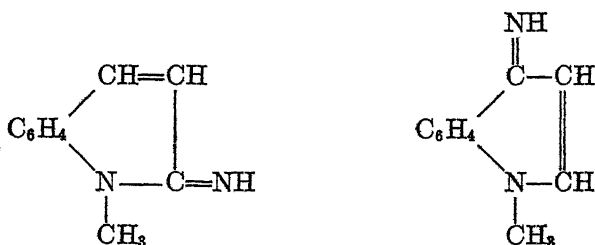
3-Aminoquinoline behaves generally as a typical aromatic amine, while 2- and 4-aminoquinolines, like the corresponding pyridine derivatives, are somewhat anomalous (*cf.* Section II, L).

2-Aminoquinoline can be hydrolyzed to the corresponding mixed ammono aquo acid ester, carbostyryl, by heating with alkali or acid (168). 2,4-Dianilinoquinoline,

$$
\begin{array}{c}
NHC_6H_5 \\
| \\
C=CH \\
\diagup \qquad | \\
C_6H_4 \\
\diagdown \qquad | \\
N=C-NHC_6H_5
\end{array}
$$
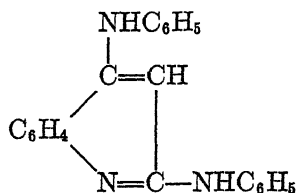
was changed successively to a mixture of phenylaminohydroxyquinolines and to 2,4-dihydroxyquinoline by heating with alcoholic potassium hydroxide at 220°C. (265). The mobility of the phenylamino groups is therefore not very high under alkaline conditions.

L. THE ACTION OF METALLOÖRGANIC COMPOUNDS ON QUINOLINE

The reactivity of the aldehydic —CH=N— group in quinoline is comparatively low because of the resonance energy associated with the six-membered ring. Nevertheless, quinoline does react with the Grignard reagent and with lithium alkyls and aryls.

(1) Sachs and Sachs (735) added quinoline to an ethereal solution of phenylmagnesium bromide and of ethylmagnesium bromide, and obtained addition compounds of the type, $C_9H_7N \cdot RMgX$, from which quinoline was regenerated on hydrolysis. The analyses were not too well in agreement with the formulas given. Oddo (642) reports also the compounds, $2C_9H_7N \cdot C_6H_5MgBr$ and $3C_9H_7N \cdot C_6H_5MgBr$, from which he prepared some 2-phenylquinoline by heating in benzene solution (641a). At a later date, this reaction was extended and 2-phenylquinoline was formed in somewhat better yield by heating an excess of phenylmagnesium bromide with quinoline in diethyl ether at 150°C. (62). Bergmann and Rosenthal (47) shook quinoline with benzylmagnesium chloride in an ether–dioxane mixture for 2 days at room temperatures, and obtained both 2-benzylquinoline and 2,4-dibenzylquinoline. The reaction mechanism has been discussed previously (Section II, F).

(2) Lithium alkyls and aryls react rapidly with quinoline to give compounds of the type

$$
\begin{array}{c}
CH=CH \\
\diagup \qquad | \\
C_6H_4 \\
\diagdown \qquad | \\
N-CHR \\
| \\
Li
\end{array}
$$
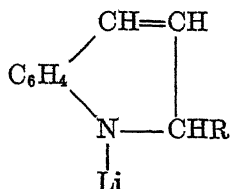
which are converted by hydrolysis into 1,2-dihydroquinolines (Li replaced by H). These can either be isolated and purified by vacuum distillation, or they may be heated with nitrobenzene and thus be oxidized to the corresponding quinoline (825a):

$$\text{C}_6\text{H}_4 \diagup^{\text{CH}=\text{CH}}_{\diagdown \text{N}=\text{CR}}$$
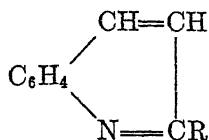
Specifically, quinoline, when treated with a 1.32 N solution of butyllithium in benzene, forms an addition product which may be hydrolyzed to give a 90 per cent yield of 2-butyl-1, 2-dihydroquinoline. Thermal decomposition of the addition compound gives 50–60 per cent of 2-butylquinoline, with elimination of lithium hydride. Phenyllithium gives principally 2-phenyl-1, 2-dihydroquinoline, with a little of the 4-phenyl derivative (825b).

Gilman and Spatz (374) treated quinoline with a slight excess of n-butyllithium in ether at −35°C. for 15 min. On hydrolysis, 2-butylquinoline was formed in 93.5 per cent yield, apparently without the formation of the expected intermediate, 2-butyl-1,2-dihydroquinoline. Subsequently (374a) it was shown that 6-methoxy-2-(4'-chlorophenyl)quinoline and related compounds could be made by the same method, but again the temperature and the time of reaction are of great importance. The lithium chlorophenyls were prepared by the action of butyllithium in ether on the chlorobromobenzenes.

<center>M. 2- AND 4-ALKYLATED QUINOLINES</center>

2-Alkylated quinolines are cyclic ammono ketone ethers, while the 4-alkylated quinolines are their vinylogues. From the numerous published reactions of quinaldine (2-methylquinoline, a "methyl ketone" of the ammonia system) and lepidine (4-methylquinoline) the following selection has been made, in order to show how closely they approach the aquo ketones in chemical behavior:

<center>*1. Deuterium interchange*</center>

Quinaldine, when heated for 60 hr. with heavy water (D_2O) at 110°C., exchanges approximately two of its side-chain hydrogens for deuterium. Benzo-[h]-quinaldine exchanges one hydrogen after 104 hr. at 110°C. but two hydrogens after 108 hr. at the same temperature in 0.02 N sodium hydroxide. Alkali therefore catalyzes the interchange, indicating that the α-hydrogen atoms of quinaldine are mobile, though of course not to the extent of the α-hydrogens of an aquo ketone (99, 473).

<center>*2. Formation of carbinols (aldol condensation)*</center>

Quinaldine condenses with 40 per cent aqueous formaldehyde at 100°C. to give 2-quinolylethanol (I) in an aldol-type condensation. By using a larger amount of formaldehyde solution, and prolonging the time of action, bis(hydroxymethyl)-quinaldine (II) and tris(hydroxymethyl)quinaldine (III) may be prepared (491, 493, 594). The reactions follow the equations below:

$$\text{C}_6\text{H}_4 \diagup^{\text{CH}=\text{CH}}_{\diagdown \text{N}=\text{CCH}_3} \qquad \text{HCHO} \qquad \text{C}_6\text{H}_4 \diagup^{\text{CH}=\text{CH}}_{\diagdown \text{N}=\text{CCH}_2\text{CH}_2\text{OH}} \qquad \text{HCHO}$$

$$C_6H_4 \diagup ^{CH=CH}_{N=\dot{C}CH(CH_2OH)_2} \quad \xrightarrow{HCHO} \quad C_6H_4 \diagup ^{CH=CH}_{N=\dot{C}C(CH_2OH)_3} \qquad (82)$$
$$\text{II} \qquad\qquad\qquad \text{III}$$
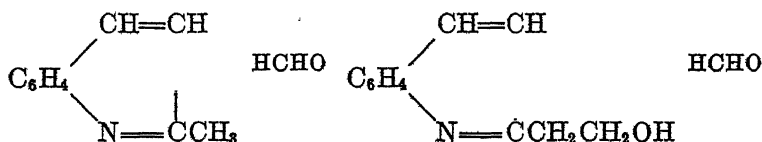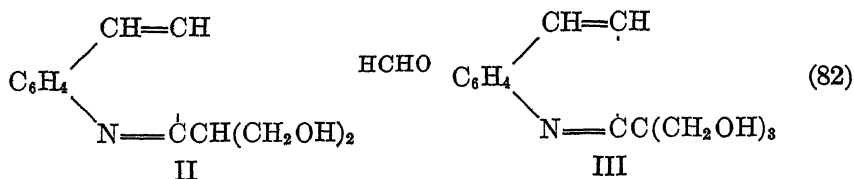
When quinaldine and chloral are heated together on the water bath, there is formed quinaldyltrichloromethylcarbinol, in accordance with the equation (274, 373, 610):

$$C_6H_4 \diagup ^{CH=CH}_{N=\ \ \dot{C}CH_3} \quad + \ CCl_3CHO \ = \ C_6H_4 \diagup ^{CH=CH}_{N=\dot{C}CH_2CH(OH)CCl_3} \qquad (83)$$
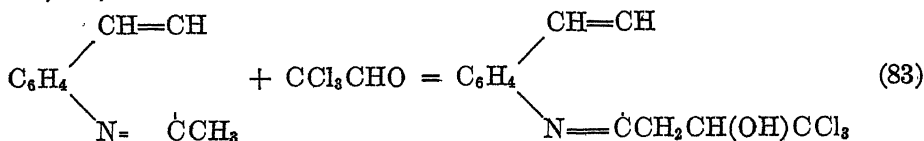
Benzaldehyde and quinaldine react in the sunlight over a period of several months to give a fair yield of phenyl(2-quinaldyl)carbinol, $C_9H_6NCH_2CH(OH)$-C_6H_5 (44a). The o-nitro derivative of the latter may be made by heating o-nitrobenzaldehyde, quinaldine, and water for 10 hr. at 85–90°C. (565b), but only a nitrostyrylquinaldine is obtained from m-nitrobenzaldehyde (790).

McElvain and Johnson (568) have condensed several ketones containing reactive carbonyl groups with quinaldine and have prepared aldol-like condensation products in the manner of the equation:

$$C_6H_4 \diagup ^{CH=CH}_{N=CCH_3} \ + \ ^{R}_{R'}\diagdown C=O \ \xrightarrow[0.25\text{--}3\ hr.]{140°C.} \ C_6H_4 \diagup ^{CH=CH}_{N=\ \ \dot{C}CH_2C-R'}^{|R}_{\diagdown OH} \qquad (84)$$
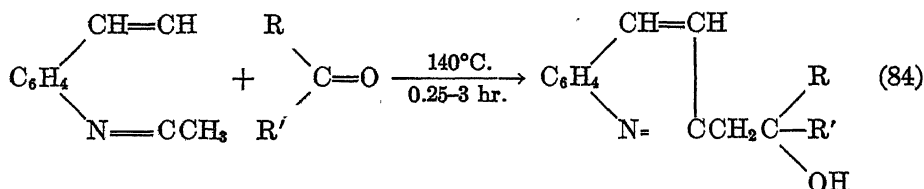
R may be —COOC₂H₅ or C₆H₅—, while R′ is C₆H₅CO—; or both R and R′ may be C₆H₅CO— or —COOC₂H₅.

Kaplan and Lindwall (449) have recently condensed quinoline-2- and -4-aldehydes (= RCHO) with quinaldine and lepidine to form the corresponding carbinols, $RCH(OH)CH_2C_9H_6N$, by an aldol-like condensation. The reaction is brought about by refluxing the components in a solvent, ethanol, for about 6 hr. with or without the addition of a catalyst, diethylamine. It is interesting that quinoline-4-aldehyde condenses with quinaldine, but not with the less reactive lepidine.

3. Formation of styryl derivatives ("Claisen reaction")

In the preceding section, quinaldine has undergone an aldol condensation with aldehydes or ketones under comparatively mild conditions. If the reactants are heated for a longer time at higher temperatures, either alone or in the presence of a catalyst such as zinc chloride or potassium acid sulfate, water is eliminated in the manner of the familiar Claisen reaction. The parallel equations are the following:

$$C_6H_5COCH_3 + C_6H_5CHO = H_2O + C_6H_5COCH=CHC_6H_5 \qquad (85)$$
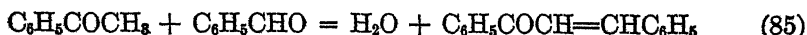
Sodium hydroxide, sodium alkoxides, acetic anhydride, or hydrochloric acid are suitable condensing agents.

$$
C_6H_4 \underset{N=CCH_3}{\overset{CH=CH}{\diagup}} + RCHO = H_2O + C_6H_4 \underset{N=CCH=CHR}{\overset{CH=CH}{\diagup}} \tag{86}
$$
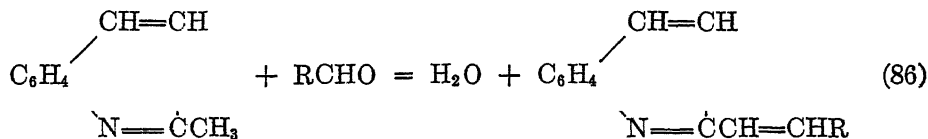
R is generally aryl.

Although zinc chloride is often used as a catalyst, as in the earlier preparations of 2-styrylquinoline (442c, 804b), it is sometimes replaced by acetic anhydride (43b, 81a, 421a; cf. 759), potassium acid sulfate (425a, 804b), or even by concentrated hydrochloric acid (640, 733). Since the 2- and 4-methylquinolines boil at a higher temperature and also are more reactive than the corresponding pyridines, it may be satisfactory to reflux the components for several hours without the use of a condensing agent, as in the preparation of the following: 2-p-dimethylaminostyryl)quinoline (640), 2-(m-nitrostyryl)quinoline (790), and 2-(2,4-dinitrostyryl)quinoline (43a). 2-Methyl-4-phenylquinoline, when heated for 4–5 hr. at 130°C. with benzaldehyde gives 2-styryl-4-phenylquinoline (306), but aldol-like condensation products (carbinols) are formed with o- and p-nitrobenzaldehydes.

Benzylidenediquinaldine, $C_6H_5CH(CH_2C_9H_6N)_2$, is a by-product of the action of benzaldehyde on quinaldine at elevated temperatures, or the main product, if 2 moles of the latter are used (392b, 421a, 491a).

In two cases, at least, it has been recorded that zinc chloride is harmful in the reaction of equation 86. John (444) finds that 2-phenyl-4-methylquinoline and benzaldehyde, when heated at 200–210°C., give 2-phenyl-4-styrylquinoline, but in the presence of zinc chloride, potassium acid sulfate, or an equimolar mixture of the two no condensation occurs. The use of a zinc chloride catalyst leads to the formation of troublesome by-products in the reaction between aldehydes and 2,4-dimethylquinoline (772a).

It has been suggested many times (115, 625, 760b) that quinaldine and lepidine react with aldehydes and other reagents in their isomeric enamic forms, I and II, respectively.

$$
C_6H_4 \underset{\underset{H}{N}\text{—}\overset{.}{C}=CH_2}{\overset{CH=CH}{\diagup}}
\qquad\qquad
C_6H_4 \underset{\underset{H}{N}\text{—}CH}{\overset{\overset{\overset{CH_2}{\|}}{C}\text{—}CH}{\diagup}}
$$

$$
\text{II}
$$
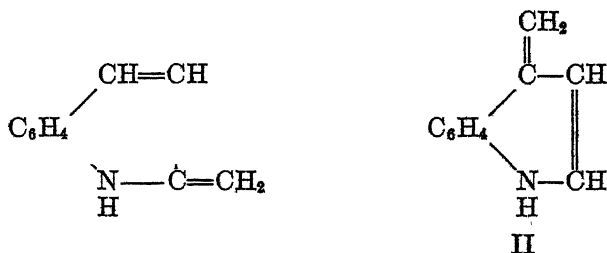
Such forms would certainly be favored by a basic environment, but many styrylquinolines are made under acid conditions. Sidgwick, Taylor, and Baker (760b) believe that zinc chloride and quinaldine react when heated to give an enamine derivative (III) that is active in the condensations.

$$CH\!=\!CH$$

$$C_6H_4 \diagdown$$

$$N\!-\!\!-\!C\!=\!CH_2$$

$$\overset{+}{Z}nCl$$

III
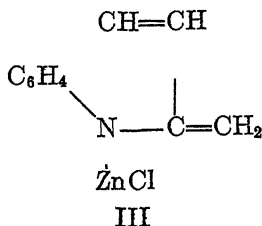
Since quaternary salts of the type of methylquinaldinium iodide (IV) are more reactive than quinaldine itself with respect to carbonyl group condensations (see Section II, I), it is possible that formation of a quinaldinium ion (V) may increase the velocity of the condensations where potassium acid sulfate or hydrochloric acid are used as catalysts.

$$\left[\begin{array}{c} CH\!=\!CH \\ C_6H_4 \diagup \\ N\!=\!\!=\!CCH_3 \\ \overset{|}{C}H_3 \end{array} \right]^{+} I^{-} \qquad \left[\begin{array}{c} CH\!=\!CH \\ C_6H_4 \diagup \\ N\!=\!\!=\!CCH_3 \\ \overset{|}{H} \end{array} \right]^{+}$$

IV   V
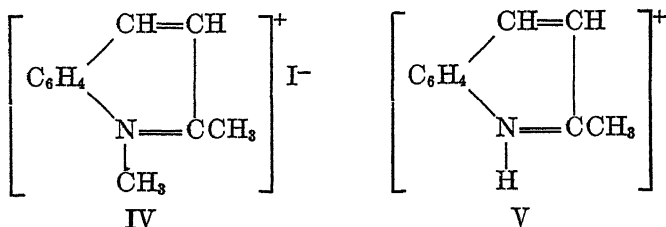
A related reaction in the water system is the hydrogen-ion (or positive-ion) catalyzed aldol condensation or Claisen reaction between an aquo aldehyde or ketone and a compound which contains reactive methylene (see Knoevenagel reaction, Section VI, A; reference 403a).

4. Reactions of lepidine and of 2,4-dimethylquinoline: comparison of reactivity of 2- and 4-methyl

Lepidine undergoes essentially the same reactions with aldehydes that have been described for quinaldine. It reacts with formalin solution to give mono- and di-methylol derivatives (493, 518), with benzaldehyde and zinc chloride at 180°C. to form 4-styrylquinoline (256, 271; cf. 498), with chloral to give an aldol-like condensation product (cf. equation 83) (610), and with quinoline-2-aldehyde, likewise to give a carbinol (449; see Section IV, M, 7).

Eibner (271), in parallel experiments, heated quinaldine and lepidine (5 g. of each) with an equal weight of benzaldehyde for 3 hr. at the boiling point; there was obtained 7.95 g. of 2-styrylquinoline and only 1 g. of the hydrochloride of 4-styrylquinoline. When an excess of formaldehyde is heated with quinaldine or lepidine, there is obtained a trimethylol derivative of the former, but only a dimethylol derivative of the latter (490a, 491; cf. 519). 2,4-Dimethylquinoline, heated with 1 mole of formaldehyde, gives 4-methyl-2-(β-hydroxyethyl)-quinoline, and with 2 moles of formaldehyde, 4-methyl-2(β,β-dihydroxyiso-propyl)quinoline (504). Chloral and 2,4-dimethylquinoline condense to form 4-methyl-2-(γ,γ,γ-trichloro-β-hydroxypropyl)quinoline or 4-methyl-2-(γ,γ,γ-trichloropropenyl)quinoline, depending upon the conditions (503, 772). 2-Styryl-4-methylquinoline may be prepared by heating equimolar parts of 2,4-dimethylquinoline and benzaldehyde (311b), while similarly the 2-methyl alone

is reactive in phthalone formation (69, 271). 2,4-Dinitrobenzaldehyde and 2,4-dimethylquinoline, when heated for 0.5 to 1 hr., give 2-dinitrostyryl-4-methyl-quinoline, while 6 to 8 hr. are required to form a 2,4-di(2,4-dinitrostyryl) derivative (44). In all of these experiments the 2-methyl has consistently proved to be more reactive than the 4-methyl, which is more distant from the activating —C=N— group. It is, however, reported that 2,4-dimethylquinoline may be oxidized by chromic acid and sulfuric acid to 2-methylquinoline-4-carboxylic acid, contrary to expectations (70). Oxidation by means of alkaline permanganate gives 4-methylpyridine-2,3,6-tricarboxylic acid, with destruction of the 2-methyl group (608a).

5. Claisen condensations

A Claisen condensation of two molecules of an aquo ester or of one molecule each of an aquo ester and and aquo ketone may be brought about by means of sodium, sodium ethoxide, and related alkoxides, or sodium amide. Claisen condensations that involve quinaldine or lepidine are effected by the same reagents.

(a) Quinophthalone is formed in almost theoretical yield by heating quinaldine and diethyl phthalate with metallic sodium (272; cf. 548). The reaction follows the equation:
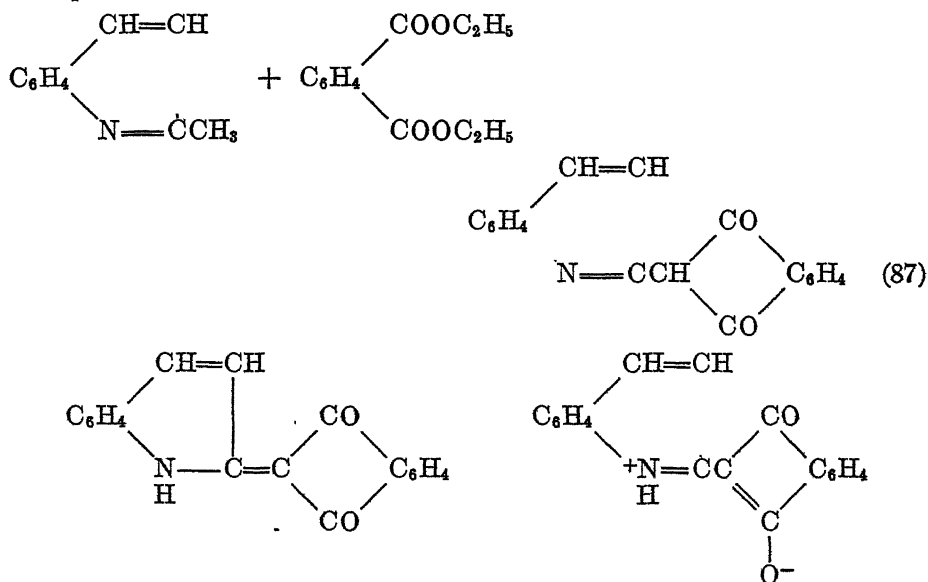
Kuhn and Bär (548) prefer one or the other of the last two formulas.

(b) Quinaldine was refluxed with potassium ethoxide and diethyl oxalate in ether or in ether–alcohol solution for about a day. The potassium salt of quinaldine oxalic ester was formed in accordance with the equation (81a, 81b, 815):

$$
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}{=}\ {=}\overset{|}{\text{C}}\text{CH(K)COCOOC}_2\text{H}_5
\end{array}
\qquad + 2\text{C}_2\text{H}_5\text{OH} \quad (88)
$$
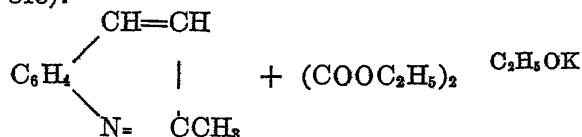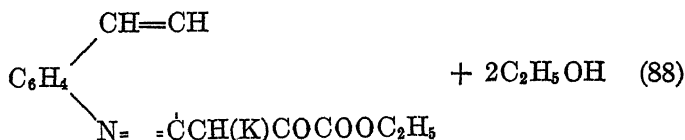
The free ester is obtained by decomposing the potassium salt with dilute sulfuric acid. A similar reaction takes place with lepidine (815).

(c) The potassium salt of quinaldine (I) reacts with an ethereal solution of an aromatic ester, in the presence of an excess of potassium amide, to give yellow ketones, as shown in the following equations (64):

$$
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}{=}\ \ \overset{|}{\text{C}}\text{CH}_3
\end{array}
\xrightarrow[\text{2.5 equiv.}]{\text{KNH}_2}
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}{=}{=}\overset{|}{\text{C}}\text{CH}_2\text{K}
\end{array}
\xrightarrow[\text{1.5 KNH}_2]{\text{C}_6\text{H}_5\text{COOC}_2\text{H}_5}
$$

$$
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}{=}{=}\overset{|}{\text{C}}\text{CHKCOC}_6\text{H}_5 \\
\text{II}
\end{array}
\quad \xrightarrow{\text{H}_2\text{O}} \quad
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}{=}\ {=}\text{CCH}_2\text{COC}_6\text{H}_5 \\
\text{III} \\
\text{2-Phenacylquinoline}
\end{array}
\qquad (89)
$$
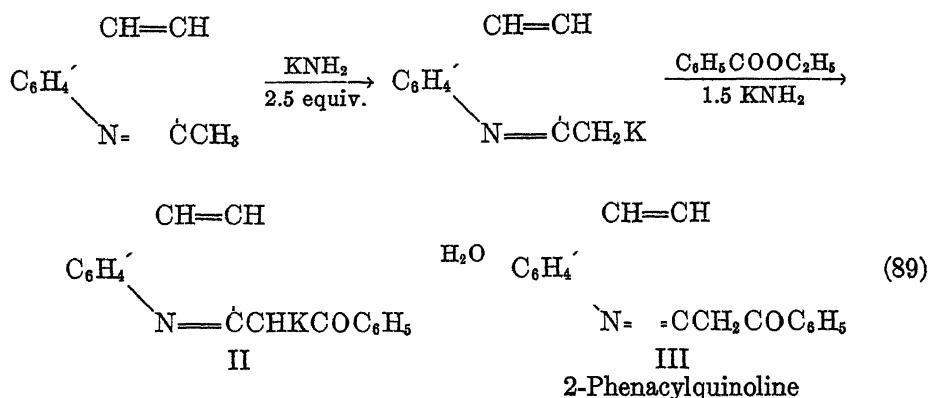
This method does not succeed with lepidine, since potassium lepidyl has too low a solubility in ether; good yields of aryl lepidyl ketones can be obtained by carrying this reaction out in liquid ammonia (317). Aliphatic esters appear to undergo metal-exchange reactions with potassium quinaldyl and potassium lepidyl, and so are unsuited for the synthesis represented by equation 89.

6. Metallic salts of quinaldine and lepidine

Quinaldine may be converted to an alkali-metal salt by treatment with phenyllithium in ether (826) (equation 90), and by the action of an alkali amide, either without solvent (118, 133) or in liquid ammonia (53, 54). Sodium and potassium salts of lepidine have similarly been made in liquid ammonia (54a).

$$
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup\quad | \\
\text{C}_6\text{H}_4 \quad | \\
\diagdown\quad | \\
\text{N}{=}\ {=}\overset{|}{\text{C}}\text{CH}_3
\end{array}
+ \text{LiC}_6\text{H}_5 \; = \; \text{C}_6\text{H}_6 \; + \;
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}{=}{=}\overset{|}{\text{C}}{-}\text{CH}_2\text{Li} \\
\Updownarrow \\
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}{-}{-}\text{C}{=}\text{CH}_2 \\
| \\
\text{Li}
\end{array}
\qquad (90)
$$

$$\begin{array}{c} CH \\ | \\ C=CH \\ C_6H_4 \\ \diagdown \\ N= CH \end{array} + NaNH_2 = \begin{array}{c} CH_2Na \\ | \\ C \quad CH \\ C_6H_4 \\ \diagdown \\ N=CH \end{array} + NH_3$$

$$\updownarrow$$

$$\begin{array}{c} CH_2 \\ \ddot{C}-CH \\ C_6H_4 \\ \diagdown \\ N-\ddot{C}H \\ | \\ Na \end{array} \qquad (91)$$
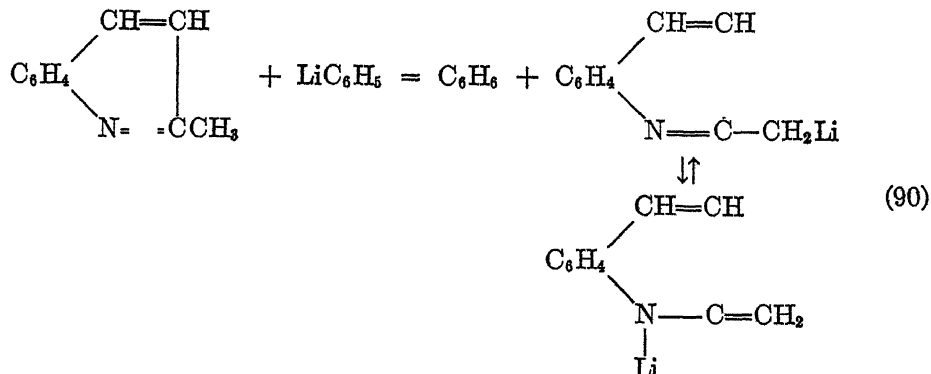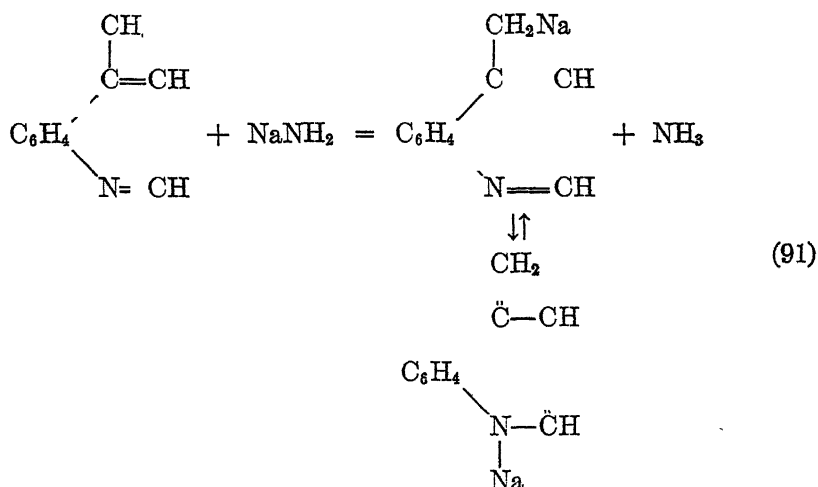
It may be presumed that the salts of quinaldine and lepidine resemble sodium acetoacetic ester in being tautomeric.

Among the reactions that have been carried out with these compounds are the following (see also section 5, just above).

Alkyl or aralkyl halides convert them to homologous quinaldines and lepidines, in accordance with the following equation (53, 118, 826):

$$\begin{array}{c} CH=CH \\ C_6H_4 \\ \diagdown \\ N= \dot{C}CH_2Na \end{array} + RX = NaX + \begin{array}{c} CH=CH \\ C_6H_4 \\ \diagdown \\ N= =\dot{C}CH_2R \end{array} \qquad (92)$$
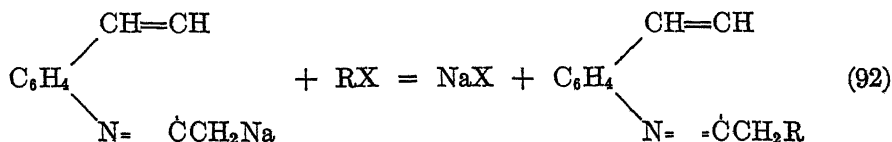
The sodium and lithium salts of quinaldine behave like a Grignard reagent in many respects, as may be seen from equation 93, which represents the formation of diphenylquinaldylcarbinol (134, 829).

$$\begin{array}{c} CH=CH \\ C_6H_4 \\ \diagdown \\ N \quad \dot{C}CH_2Li(Na) \end{array} + (C_6H_5)_2CO =$$

$$\begin{array}{c} CH=CH \\ C_6H_4 \\ \diagdown \\ N= \dot{C}CH_2C-C_6H_5 \\ \diagdown \\ C_6H_5 \end{array} \xrightarrow{H_2O} \begin{array}{c} CH=CH \\ C_6H_4 \\ \diagdown \\ N= \dot{C}CH_2C-C_6H_5 \\ \diagdown \\ C_6H_5 \end{array} \qquad (93)$$
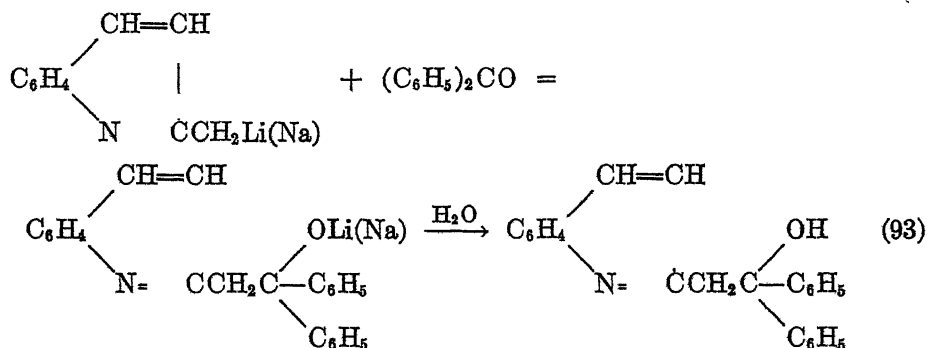
While the enamic forms of quinaldine and lepidine, corresponding to the alternate structures of the metallic salts given in equations 90 and 91, have never been isolated, both di- and tri-quinolylmethanes exist in two modifications, one of which is red, and the other colorless (740a, 741, 742).

$$\begin{array}{ccc}
\text{CH=CH} \backslash & & \\
\text{C}_6\text{H}_4 \diagup \quad \text{CH} & & \\
\text{N=}\dot{\text{C}}\text{--} \diagup _3 & & \\
\end{array}$$

(colorless)

$$\left(\begin{array}{c}
\text{CH=CH'} \\
\text{C}_6\text{H}_4 \diagup \\
\text{N=}\quad \dot{\text{C}}\text{--} \diagup _2
\end{array} \right) = \text{C=}\dot{\text{C}} \quad \begin{array}{c} \text{CH=CH} \\ \diagdown \text{C}_6\text{H}_4 \\ \text{-NH} \diagup \end{array}$$

(red)

Tri-2-quinolylmethane

7. Oxidation with selenium dioxide

Methyl ketones of the oxygen system react with selenium dioxide when heated to form α-ketoaldehydes, in the manner of the following equation (704):

$$\text{SeO}_2 + \text{C}_6\text{H}_5\text{COCH}_3 = \text{C}_6\text{H}_5\text{COCHO} + \text{H}_2\text{O} + \text{Se} \qquad (94)$$

Henze (420), in an attempt to extend these reactions to the pyridine and quinoline series, refluxed 2-picoline, quinaldine, and a number of related compounds with selenium dioxide, and obtained the corresponding carboxylic acid ($\text{CH}_3 \rightarrow$ COOH), together with smaller quantities of the aldehyde. In this fashion, 2-ethyl-3-methylquinoline is oxidized by selenium dioxide to 3-methylquinoline-2-carboxylic acid, with the destruction of the alkyl group directly attached to —C=N—.

Other workers have had better success with the selenium dioxide method for the preparation of quinoline-2- and -4-aldehydes. Kaplan (448), in repeating earlier work of Kwartler and Lindwall (549) along similar lines, found that the selenium dioxide should be freshly prepared just prior to use as an oxidant; if this is done, the yields of aldehyde will reach 58 per cent of the theoretical. If, on the other hand, the selenium dioxide had been stored unsublimed for several months, it converted quinaldine into a benzoin-type compound, quinaldoin (I), and lepidine into the ethylenic derivative (II). Possible equations are the following:

$$\begin{array}{c}
\text{CH=CH} \\
\text{C}_6\text{H}_4 \diagup \quad | \\
\text{N=CCH}_3
\end{array} + \begin{array}{c}
\text{CH=CH} \\
\text{C}_6\text{H}_4 \diagup \quad | \\
\text{N=CCHO}
\end{array} \xrightarrow[\text{condensation}]{\text{aldol}}$$

$$\begin{array}{c}
\text{CH=CH} \qquad\qquad \text{CH=CH} \\
\text{C}_6\text{H}_4 \diagup \quad | \qquad\qquad | \quad \diagdown \text{C}_6\text{H}_4 \\
\diagdown \text{=CCH}_2\text{CH(OH)}\text{C}\text{=}\text{N} \diagup
\end{array} \xrightarrow[\text{SeO}_2]{\text{(O)}}$$

$$\begin{array}{c}
\text{CH=CH} \qquad\qquad \text{CH=CH} \\
\text{C}_6\text{H}_4 \diagup \quad | \qquad\qquad | \quad \diagdown \text{C}_6\text{H}_4 \cdot \quad (95) \\
\text{N=CCOCH(OH)}\text{C}\text{=}\text{N}
\end{array}$$

I

$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}{=}\text{CH} \\
\text{C}_6\text{H}_4 \quad\quad\quad | \\
\text{N}{=}\text{CH}
\end{array}
\;+\;
\begin{array}{c}
\text{CHO} \\
| \\
\text{C}{=}\text{CH} \\
\text{C}_6\text{H}_4 \quad\quad\quad | \\
\text{N}{=}\text{CH}
\end{array}
\;=\;
$$

$$
\begin{array}{c}
\text{CH}{=\!=\!=\!=\!=\!=}\text{C} \\
| \quad\quad\quad\quad\quad\quad | \\
\text{C}{=}\text{CH} \quad\quad \text{CH}{=}\text{C} \\
\text{C}_6\text{H}_4 \quad\quad\quad\quad\quad\quad\quad \text{C}_6\text{H}_4 \;+\; \text{H}_2\text{O} \quad (96)\\
| \quad\quad\quad\quad\quad\quad | \\
\text{N}{=}\text{CH} \quad\quad \text{CH}{=}\text{N}
\end{array}
$$

<div align="center">II</div>

2,3,8-Trimethylquinoline has similarly been oxidized to 3,8-dimethylquinoline-2-aldehyde, in 82 per cent yield (105b).

8. Quinaldine and bromine

Quinaldine reacts with bromine to form ω,ω,ω-tribromoquinaldine, $C_9H_6NCBr_3$, which is converted to quinaldic acid, C_9H_6NCOOH-2, when heated with 1:10 sulfuric acid (404). The analogous replacement of the α-hydrogen atoms of an aquo ketone by halogen generally takes place readily.

9. The Mannich reaction

An aquo ketone containing a reactive methyl or methylene group reacts with formaldehyde and a primary or secondary amine in accordance with the representative equation (74, 578):

$$
C_6H_5COCH_3 + HCHO + (CH_3)_2NH \cdot HCl = C_6H_5COCH_2CH_2N(CH_3)_2 \cdot HCl + H_2O \quad (97)
$$
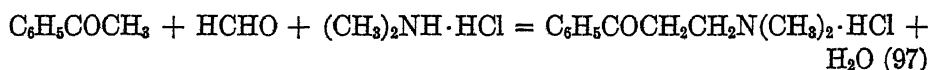
Quinaldine, 2-picoline, 2-ethoxy-4-methylquinoline, and a few related compounds have been similarly condensed with formaldehyde and primary or secondary amine hydrochlorides (288c, 289, 472, 663) in the manner of the equation below:

$$
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \quad\quad\quad + \text{CH}_2\text{O} + (C_2H_5)_2NH \cdot HCl = \\
\diagdown \\
\text{N}{=\!=}\overset{\cdot}{\text{C}}\text{CH}_3
\end{array}
$$

$$
\begin{array}{c}
\text{CH}{=}\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \quad\quad\quad\quad\quad\quad\quad\quad (98)\\
\diagdown \\
\text{N}{=\!=}\overset{\cdot}{\text{C}}\text{CH}_2\text{CH}_2\text{N}(C_2H_5)_2 \cdot HCl + H_2O
\end{array}
$$

<div align="center">I</div>
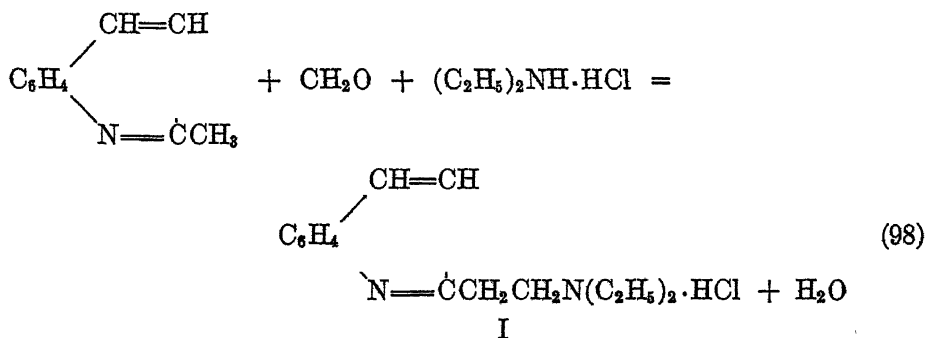
Formaldehyde (9 g. of 37.5 per cent solution) was added slowly to a mixture of diethylamine hydrochloride (10.9 g.), water (9 g.), alcohol (8 g.), and quinaldine (14.5 g.), and the mixture heated for about 2 hr. at 60°C. The reaction product colored in the air and soon resinified, but the related compound obtained from formaldehyde, lepidine, and diethylamine hydrochloride is more stable (288c).

Tseou Heou-Feo (288c) has shown that the most probable mechanism is the following:

$$CH_2O \ + \ (C_2H_5)_2NH \cdot HCl \ = \ CH_2\overset{\displaystyle OH}{\underset{\displaystyle N(C_2H_5)_2 \cdot HCl}{\big<}}$$

$$II$$

$$C_6H_4\overset{\displaystyle CH=CH}{\underset{\displaystyle N=CCH_3}{\big<}} \ + \ CH_2\overset{\displaystyle OH}{\underset{\displaystyle N(C_2H_5)_2 \cdot HCl}{\big<}}$$

$$II$$

$$, \ C_6H_4\overset{\displaystyle CH=CH}{\underset{\displaystyle N=CCH_2CH_2N(C_2H_5)_2 \cdot HCl}{\big<}} \ + \ H_2O \qquad (99)$$

$$I$$
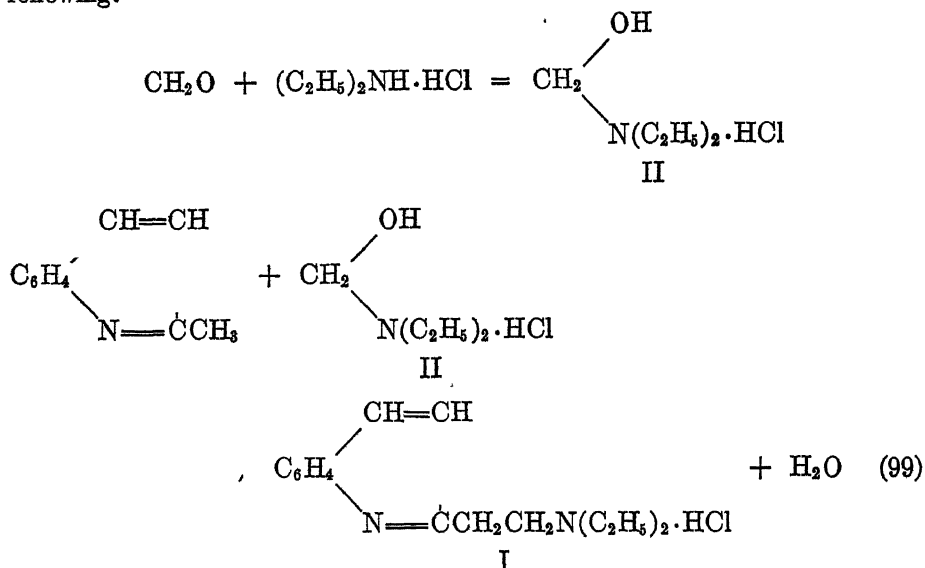
Formaldehyde and diethylamine hydrochloride condense to form the hydrochloride of diethylaminomethyl alcohol (II), which has a very readily replaceable hydroxyl group since it is an ammono aquo meroacetal (cf. Sections I, E and VI). Hydrochloric acid is a necessary catalyst in the reaction, suggesting that the ions, $\overset{+}{CH_2}=OH$ or $CH_2=\overset{+}{N}(C_2H_5)_2$, might be intermediates.

N. QUATERNARY QUINOLINIUM SALTS

Quinoline adds alkyl iodides, alkyl bromides, and some alkyl chlorides and esters of the type of methyl sulfate or methyl p-toluenesulfonate to form quaternary ammonium salts, as is shown in the equation below:

$$C_6H_4\overset{\displaystyle CH=CH}{\underset{\displaystyle N=CH}{\big<}} \ + \ CH_3I \ = \ C_6H_4\overset{\displaystyle CH=CH\rceil}{\underset{\displaystyle \underset{\displaystyle CH_3}{\overset{\displaystyle |}{N=CH}}}{\big<}} \quad I^- \qquad (100)$$
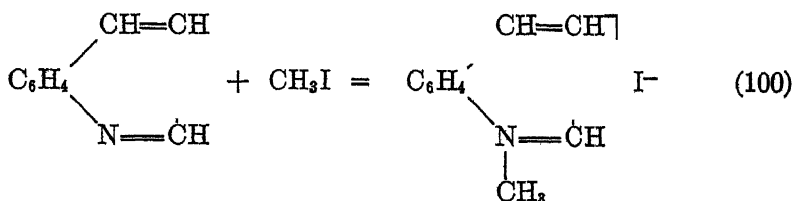
It has been pointed out previously in connection with the quaternary pyridinium salts (Section II, I) that the positive charge on the cation, while chiefly on the

nitrogen, may resonate to the 2- and 4-positions, and increase the aldehydic or ketonic reactivity of the molecule as a whole.   Therefore in many respects the study of these salts as representatives of a nitrogen system of compounds is of particular interest, as will be seen from the numerous examples that are given below.

1. Quinoline alkiodides and potassium cyanide

Quinoline methiodide and related salts when treated with an aqueous solution of potassium cyanide give 1-alkyl-4-cyano-1,4-dihydroquinolines in good yield. These are oxidized by iodine in methanol containing pyridine to 4-cyanoquinoline alkiodides, and the latter, when heated, are converted to 4-cyanoquinoline and an alkyl iodide.   The reactions are expressed by the following equations:
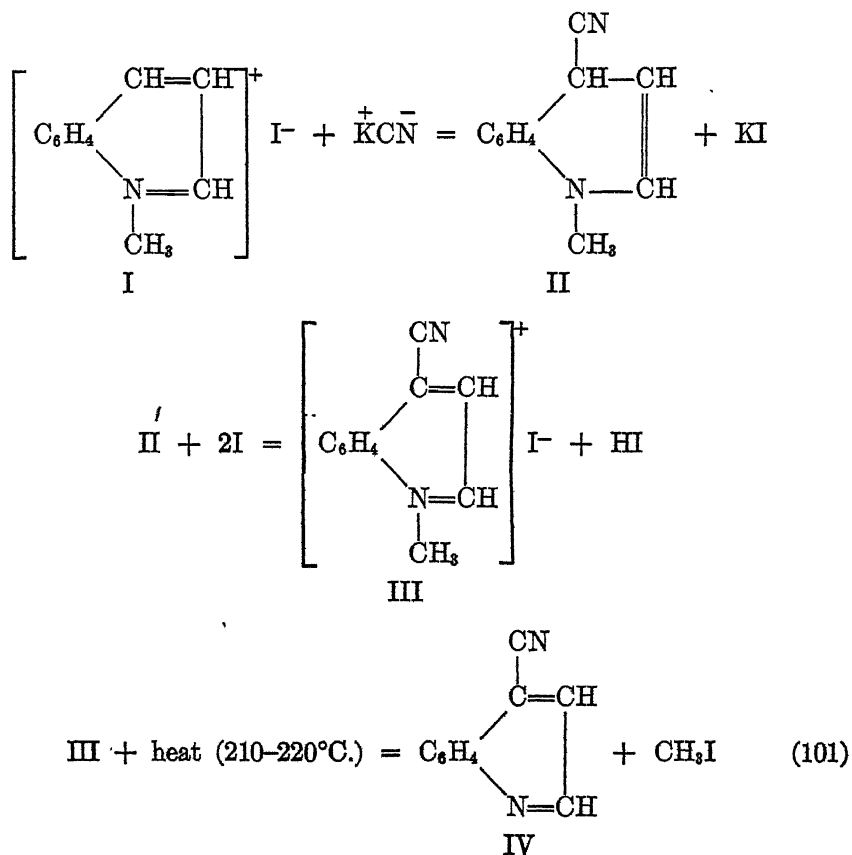
Just why the cyanogen group is attached to the 4-carbon in this reaction, and to the 2-carbon in the product obtained by treating quinoline and benzoyl chloride with potassium cyanide, is not known, but it may be connected with the difference in the polar character of the methyl and benzoyl groups (451, 454, 468, 520) (see also Section IV, F; cf. Section IV, N, 9, b, (1)).

2. Formation of pseudo bases

The reaction of quaternary quinolinium salts with the strongly basic hydroxyl ion follows the course of equation 102 below:

$$\underset{\overset{|}{CH_3}}{\overset{CH=CH}{C_6H_4}} I^- + NaOH \quad \underset{\overset{|}{CH_3}}{\overset{CH=CH^-}{C_6H_4}} OH^- + NaI \quad (102)$$

$$II \rightleftarrows \underset{\overset{|}{CH_3}}{\overset{CH=CH}{C_6H_4}}\overset{}{N-CHOH}$$

III
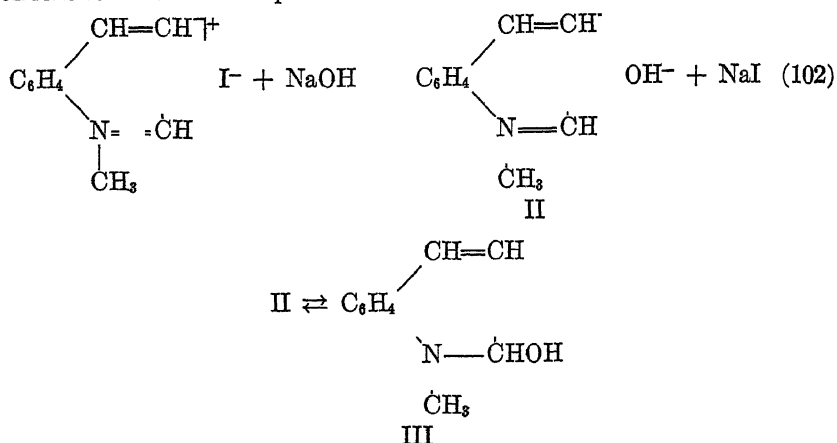
When alkali is added to an aqueous solution of quinoline methiodide, there results an equilibrium mixture of N-methylquinolinium ion, sodium ion, hydroxyl ion, and iodide ion. The solution can be said to contain the true (strong) quaternary ammonium base (II), but this is in equilibrium with the pseudo base (III), in which the hydroxyl has become attached to the 2-carbon atom.

In connection with pseudo bases of the pyridine series (Section II, I, 7), it was shown that substances of the type of III are cyclic ammono aquo meroacetals, comparable with an aldehyde alcoholate of the water system, $CCl_3CH(OH)OC_2H_5$. The relationship of the pseudo bases to the aldehyde hydrates and to aldehyde ammonias of the constitution $RCHOHNH_2$, has been clearly pointed out by Decker and Kaufmann (220; *cf.* 63), who also call attention to the fact that the change II → III is analogous to the decomposition of ammonium hydroxide into ammonia and water (215).

Hantzsch and Kalb (407) were the first to investigate with any thoroughness the reactions expressed by equation 102. An aqueous solution of methylquinolinium iodide was digested with an excess of silver oxide (409a) and the changes followed titrimetrically. The titre of the filtrate from the silver iodide–silver oxide precipitate, while high at first, steadily fell because of the precipitation of an insoluble ether of the composition IV (see also 200, 218, 459).

$$2\underset{\overset{|}{CH_3}}{\overset{CH=CH}{C_6H_4}}N-CHOH = \underset{\overset{|}{CH_3}}{\overset{CH=CH}{C_6H_4}}N-CH-O-CH-N\overset{CH=CH}{C_6H_4} + H_2O \quad (103)$$

III   IV
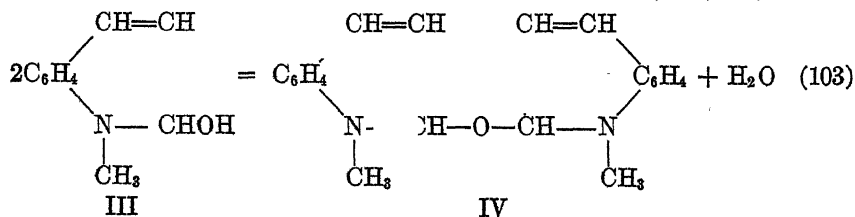
Therefore, it is this ether that is the cause of the slowly developing cloudiness when alkali is added to a solution of quinoline methiodide in water at room temperatures (409a). In benzene or alcohol solution, IV is easily decomposed with the formation of reddish "smears" and resins, while hydrochloric acid in water converts it to N-methylquinolinium chloride, a salt of the true base (II). If the same reaction is carried out in benzene under anhydrous conditions, there is obtained a reddish precipitate containing more chlorine than the salt, into which it passes when treated with water.

Aston and coworkers (17, 18) consider that the point of equilibrium in the reaction, II → III, lies far over on the left, in favor of the true base, since pseudo bases appear to form in quantity only when the conjugation of an aromatic six-membered ring is not broken. The mechanism of ether formation from the pseudo base is regarded as the following:

$$\left[RN{=}CR' \right]^{+} + OH^{-} \rightleftarrows RN{-}C(OH)R'$$
$$\text{Pseudo base} \tag{104}$$

$$RN{-}C(OH)R' + OH^{-} \rightleftarrows \left[RN{-}C(O)R' \right]^{-} + H_2O$$
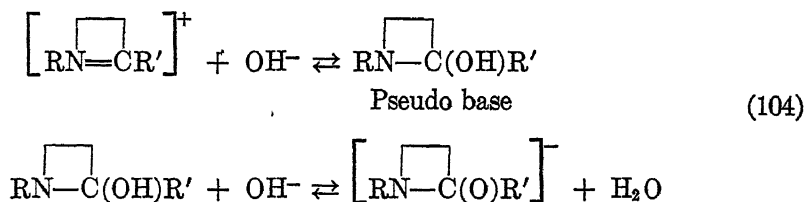
Both of the above equilibria are established rapidly. The quaternary ammonium cation and the negative alkoxide ion then react more slowly to form the ether, as shown in the equation:

$$\left[RN{=}CR' \right]^{+} + \left[RN{-}C(O)R' \right]^{-} = \left[RN{-}C{-}R' \right]_2 O \tag{105}$$
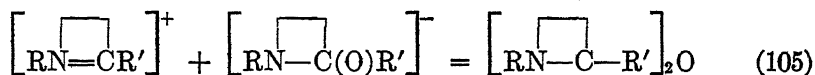
The hydroxyl group in the pseudo bases, or 1-alkyl-2-hydroxy-1,2-dihydroquinolines, is very mobile (220, 460) and may be readily replaced by other groups, as will be seen from the examples listed below (*cf.* also cotarnine and hydrastinine in Sections V, I and J). Many investigators (216, 371a, 371b, 458, 707, 729) believe that the high reactivity of this class of compounds is best explained on the basis of an open-chain amino aldehyde formula,

$$C_6H_4 \underset{\diagdown NHCH_3}{\overset{\diagup CH{=}CHCHO}{}}$$
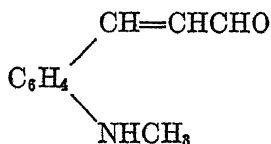
although the evidence seems to point to the correctness of the cyclic form (216). An equilibrium between the two is not excluded, since the related meroacetal (hemiacetal), glucose, appears to exist as an open-chain aldehyde in an amount not exceeding a few tenths of 1 per cent.

(a) When the pseudo bases are crystallized from alcohol, they react to form the corresponding alcoholate, or "oxygen ether", in accordance with the equation:

$$C_6H_4 \underset{\underset{\underset{VI}{R}}{\overset{|}{N}-\overset{|}{C}HOH}}{\overset{\overset{CH=CH}{\diagup}}{\diagup}} + R'OH = C_6H_4 \underset{\underset{\underset{VII}{R}}{\overset{|}{N}-\overset{|}{C}HOR'}}{\overset{\overset{CH=CH}{\diagup}}{\diagup}} + HOH \quad (106)$$
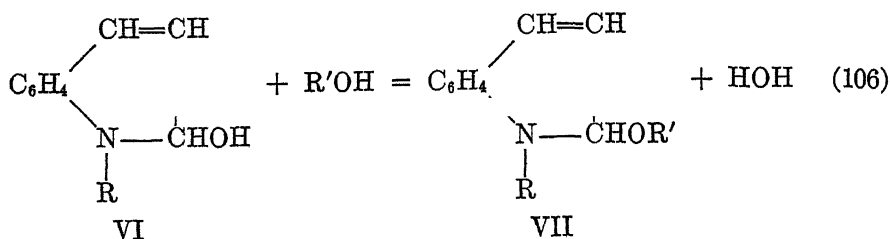
A cyclic ammono aquo meroacetal has been converted to a cyclic ammono aquo acetal (VII). Crystallization of the latter from another alcohol will replace R' by the group derived from that alcohol (188a, 201, 371d, 458).

Related changes of the water system are known, since chloral alcoholate, $CCl_3CH(OH)OC_2H_5$ reacts reversibly with alcohols to form ethanol and another chloral alcoholate (371e, 548a). Aquo acetals probably would require acid catalysts to effect such an interchange reaction under mild conditions.

(b) Decker and Kaufmann (219) believe that the cyanines owe their formation to the reactivity of these carbinols or pseudo bases, in a manner more fully developed in Section IV, N, 9. It may be said in passing that some of the reactions are related rather closely to the aldol condensation between an aldehyde and a ketone, the ketones in question being the quaternary quinaldinium or lepidinium salts. In view of the earlier discussion of pyridine alkiodides (Section II, I), it is clear that the positive charge on the cation of a quaternary quinolinium salt will increase the aldehydic or ketonic reactivity of the linkages, respectively,

$$-CH=N- \quad \text{or} \quad -\underset{\underset{CH_3}{|}}{C}=N-$$
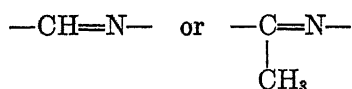
particularly in those reactions which concern a basic anion. The question as to whether the positive quinaldinium ion or the pseudo base is involved in a particular condensation is somewhat akin to a decision as to whether or not an aldehyde in water solution reacts as the free aldehyde, or as the aldehyde hydrate, or in alcoholic solution as the hemiacetal. It is possible that both forms are reactive but under different experimental conditions. Decker and Kaufmann (221) have already speculated upon this possibility.

Open-chain equivalents of a pseudo base, or ammono aquo meroacetal, may sometimes be prepared by the addition of an amine to an aldehyde, in the manner of the following equation (290, 570, 777):

$$R'CHO + R_2NH = R'CH \underset{\underset{I}{\diagdown NR_2}}{\overset{\diagup OH}{}} \rightleftarrows \underset{II}{[R'CH=\overset{+}{N}R_2]OH^-} \quad (107)$$
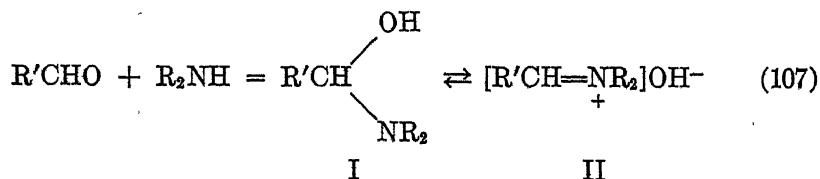
The high reactivity of the known representatives of this class of compounds has led many investigators to assume that they are intermediates in amine-catalyzed

condensations of the type of Knoevenagel reaction. Within recent years, there has been a tendency to consider that other mechanisms are the more probable (see Section VI, A, 1).

At the time of the appearance of the paper of Decker and Kaufmann (221), Hope and Robinson (436; cf. 715a) explained the function of the secondary amine as a catalyst in the following manner: The addition compound (I) formed by the action of a secondary amine on an aldehyde or ketone is an open-chain pseudo base, which is believed to be in equilibrium with the true base (II), at least in an ionizing solvent such as water. The cation of II may be considered a specialized type of ammono aldehyde ether, of very high reactivity toward basic anions, such as are derived from compounds with reactive methylene. Related cyclic compounds are the quaternary pyridinium and quinolinium hydroxides (cf. Section IV, N, 9, b, (1)). The positive ion of II can unite with the negative residue of HX, where X is CN, —CH$_2$NO$_2$, —CH$_2$C$_6$H$_3$(NO$_2$)$_2$, etc., to give
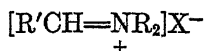
$$[R'CH \!=\! \overset{+}{N}R_2]X^-$$

which is unstable and soon becomes R'CHNR$_2$. The latter is stable if X is CN,

$$\overset{\mid}{X}$$

but if X contains a reactive methylene group, dialkylamine may be lost (i.e., the catalyst is regenerated) to form a condensation product, such as R'CH$=$CHNO$_2$ or R'CH$=$CHC$_6$H$_3$(NO$_2$)$_2$.

It is possible for a system of the structure $R\overset{\alpha}{CH_2}CH \!=\! \overset{+}{N}R_2$ to add to a carbonyl group or to its ammonia system equivalent, —C$=$N—, since the ionization of a hydrogen in the α-position will be favored by the positive charge on the nitrogen ($-I$ effect).

In summarizing, it may be said that the chemistry of the pseudo bases can be explained on the basis of either the carbinol or the quaternary ammonium hydroxide formulas.

Many reactions of an aquo aldehyde or ketone, including the aldol condensation, are catalyzed by the hydrogen ion, which is generally assumed to add to the carbonyl oxygen to form an oxonium ion, as shown in the equation below (cf. 83a, 403a):

$$R_2C \!=\! O + H^+ \rightarrow R_2C \!=\! \overset{+}{O}H \qquad (110a)$$
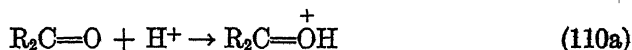
The positive charge on the oxygen will function as does the positive charge on the nitrogen in the cases just discussed and will increase carbonyl reactivity, as with the oxonium salts that are mentioned in Section III. It is possible that quinoline ring closures that depend upon the reaction between an aldehydic terminal of a side chain and an ortho hydrogen of the ring are catalyzed in this manner (see Section IV,A; compare the formation of triphenylmethane dyes from phenols or dialkylanilines and aromatic aldehydes or ketones in the presence of zinc chloride or phosphorus oxychloride).

(c) Quinoline methiodide is- converted by an excess of warm alkali into a mixture of 1-methyl-2-quinolone (III) and 1-methyl-1,2,3,4-tetrahydroquinoline (IV), in accordance with the equation (191):

$$
\left[C_6H_4 \underset{\substack{| \\ CH_3}}{\overset{CH=CH}{\underset{N=CH}{\Big|}}} \right] I^- + 3NaOH \rightleftharpoons 3C_6H_4 \underset{\substack{| \\ CH_3}}{\overset{CH=CH}{\underset{N-CHOH}{\Big|}}} \xrightarrow[\text{warm}]{\text{NaOH}}
$$

$$
2C_6H_4 \underset{\substack{| \\ CH_3}}{\overset{CH=CH}{\underset{N-C=O}{\Big|}}} + C_6H_4 \underset{\substack{| \\ CH_3}}{\overset{CH_2-CH_2}{\underset{N-\ \ CH_2}{\Big|}}} \qquad (108)
$$

$$
\text{III} \qquad\qquad \text{IV}
$$
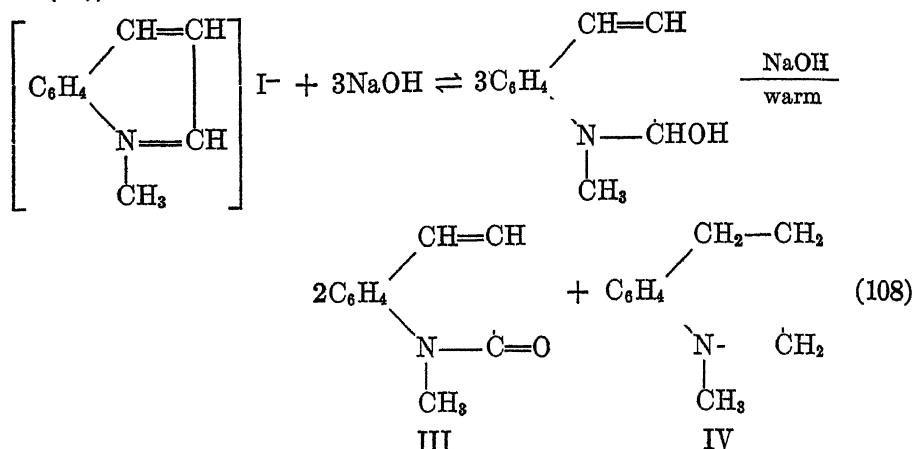
The yields do not appear to be very good. Since 1-methyl-2-quinolone (III) is a cyclic ammono aquo ester, and since 1-methyl-1,2,3,4-tetrahydroquinoline (IV) is a cyclic ammono ether, the reaction of equation 108 is related to the Cannizzaro reaction below, though not strictly comparable.

$$
2C_6H_5CHO + NaOH(\text{conc.}) = C_6H_5COONa + C_6H_5CH_2OH \qquad (109)
$$

(d) Oxidation of an alkaline solution of a quinolinium salt—which contains a small amount of pseudo base—leads to the formation of a 1-alkyl-2-quinolone, as shown in the equation below:

$$
C_6H_4 \underset{\substack{| \\ CH_3}}{\overset{CH=CH}{\underset{N-CHOH}{\Big|}}} + (O) = H_2O + C_6H_4 \underset{\substack{| \\ CH_3}}{\overset{CH=CH}{\underset{N-C=O}{\Big|}}} \qquad (110)
$$
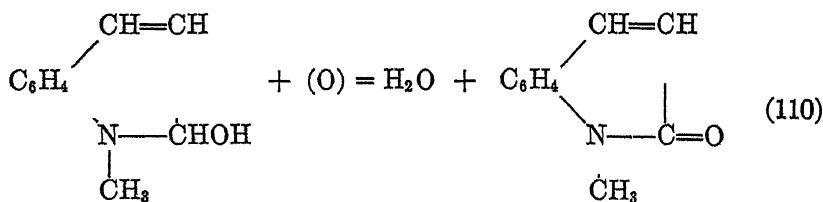
· The oxidation is accomplished by potassium ferricyanide in alkaline solution, or electrolytically (188, 197, 202, 210, 294, 308, 684). A cyclic ammono aquo meroacetal (the pseudo base) is oxidized to a cylic ammono aquo ester.

3. Quaternary salt of cinchoninic acid ester

The iodomethylate of the ethyl ester of cinchoninic acid (I) when treated with alkali or ammonia gives a thick dirty white precipitate, probably of the pseudo or carbinol base. This dissolves slowly in excess of alkali at ordinary temperatures. When treated with potassium iodide and acid, there is obtained the methiodide of cinchoninic acid, indicating that quaternary salt formation has increased the rate of saponification of the ester (232).

$$
\begin{bmatrix}
\quad\quad COOC_2H_5 \\
\quad\quad C{=}CH \\
C_6H_4 \\
\quad\quad N{=}CH \\
\quad\quad CH_3
\end{bmatrix}^+
I^- \quad \xrightarrow[\text{then KI + acid}]{\text{NaOH}} \quad
\begin{bmatrix}
\quad\quad COOH \\
\quad\quad C{=}CH \\
C_6H_4 \\
\quad\quad N{=}CH \\
\quad\quad CH_3
\end{bmatrix}^+
I^- \quad (111)
$$

I
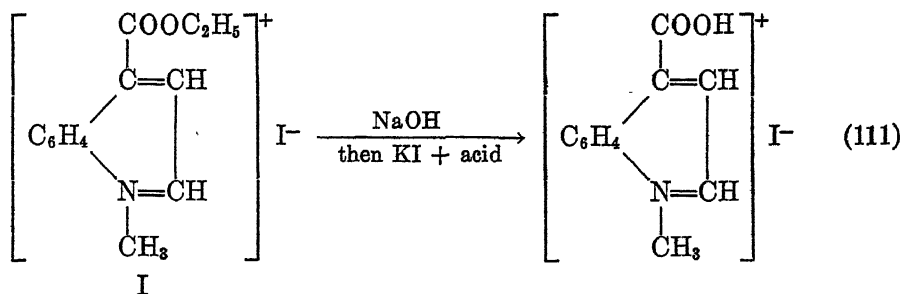
4. Quinoline alkiodides and the Grignard reagent

The Grignard reagent reacts with quinoline alkyl halides in ether to form 1,2-dialkyl-1,2-dihydroquinolines in good yields in accordance with the equation (84, 332, 338, 341, 592, 593):

$$
\begin{bmatrix}
\quad\quad CH{=}CH \\
C_6H_4 \\
\quad\quad N{=}CH \\
\quad\quad CH_3
\end{bmatrix}
I^- + RMgX = MgXI + C_6H_4
\begin{array}{c}
CH{=}CH \\
\\
N{-}\quad CHR \\
CH_3
\end{array}
\quad (112)
$$

II
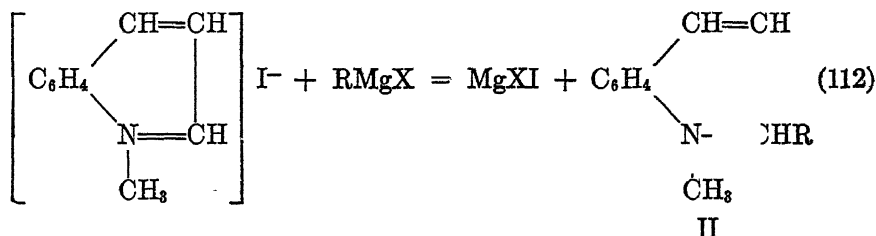
Quinoline methiodide (I), here regarded as a specialized type of aldehyde (see Sections II, I; IV, N), has been converted by the Grignard reagent to a cyclic ammono ether (II). The latter may often be thermally decomposed to a hydrocarbon and a 2-substituted quinoline, as in the specific example below (592a; cf. 338):

$$
C_6H_4
\begin{array}{c}
CH{=}CH \\
\\
N{-}CHC_3H_7\,(n) \\
CH_3
\end{array}
\quad \xrightarrow{\text{heat}} \quad CH_4 + C_6H_4
\begin{array}{c}
CH{=}CH \\
\\
N{=}CC_3H_7\,(n)
\end{array}
\quad (113)
$$
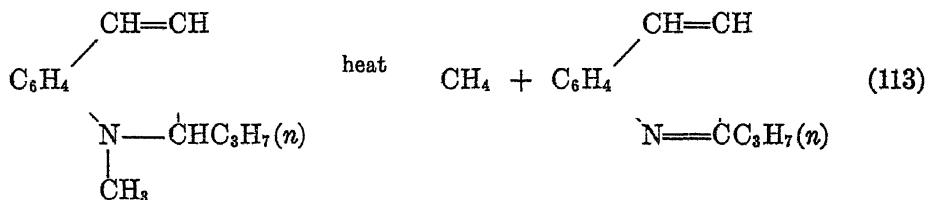
5. The alkiodides of quinaldine and lepidine

Quaternary salt formation not only increases the aldehydic reactivity of quinoline, but also the ketonic reactivity of quinaldine and lepidine, as the following illustrations will show:

(a) Quinaldine methiodide is mixed with the theoretical quantity of p-dimethylaminobenzaldehyde and dissolved in alcohol by short warming. A few drops of piperidine are added, and the mixture refluxed for 2–3 hr., whereupon the methiodide of p-dimethylaminostyrylquinoline is formed (514, 734; cf. 620):

$$
\begin{array}{c}
\text{CH}=\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}=\overset{|}{\text{C}}-\text{CH}_3 \\
| \\
\text{CH}_3
\end{array}
\quad \text{I}^- + p\text{-}(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{CHO} = \text{H}_2\text{O} +
$$

$$
\begin{array}{c}
\text{CH}=\text{CH} \\
\diagup \\
\text{C}_6\text{H}_4 \\
\diagdown \\
{}^+\text{N}=\overset{|}{\text{C}}\text{CH}=\text{CHC}_6\text{H}_4\text{N}(\text{CH}_3)_2 \\
| \\
\text{CH}_3
\end{array}
\quad \text{I}^- \qquad (114)
$$
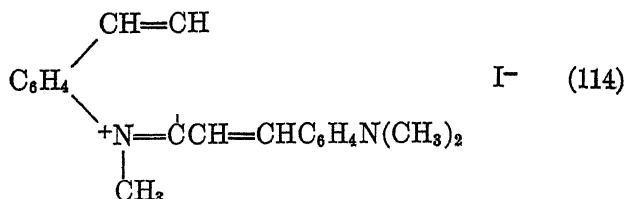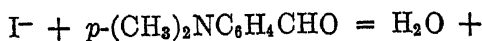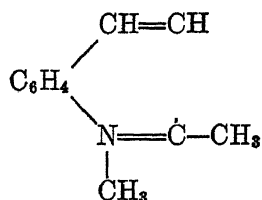
König and Treichel (516) remark that this condensation goes especially readily with p-aminobenzaldehyde, but less readily with the ortho isomer. Quinaldinium salts in general react sensibly faster than lepidinium salts, and both are much more reactive than the free heterocycles, showing the great activating influence of the positive charge on the cation. Within comparatively recent years there have been prepared a large number of substituted styrylquinoline alkiodides (19, 35, 95, 173, 184, 184c, 399, 400, 474, 516, 596, 655a, 711b).

According to Mills, Smith, and Raper (617, 625; cf. 760b) the mechanism of the reaction of equation 114 is the following: Quinaldine methiodide, to take a specific example, reacts with the small amount of piperidine or other secondary amine used as a catalyst to form some 1-methyl-2-methylene-1,2-dihydroquinoline (II) (a "methylene base"), which condenses with dimethylaminobenzaldehyde to give an allenic compound (III). This abstracts hydrogen iodide from piperidine hydroiodide to form the final product, 2-(p-dimethylaminostyryl)-quinoline methiodide (IV), with regeneration of the catalyst, piperidine. The equations are the following:

$$
\left[
\begin{array}{c}
\text{CH}=\text{CH} \\
\diagup \quad | \\
\text{C}_6\text{H}_4 \quad | \\
\diagdown \quad | \\
\text{N}=\overset{|}{\text{C}}\text{CH}_3 \\
| \\
\text{CH}_3
\end{array}
\right]^+ \text{I}^- + \text{C}_5\text{H}_{10}\text{NH} = \text{C}_5\text{H}_{10}\text{NH}\cdot\text{HI} +
$$

$$
\text{I}
$$

$$
\begin{array}{c}
\text{CH}=\text{CH} \\
\diagup \quad | \\
\text{C}_6\text{H}_4 \\
\diagdown \\
\text{N}\text{---}\text{C}=\text{CH}_2 \\
| \\
\text{CH}_3
\end{array}
$$

$$
\text{II}
$$

$$\text{II} + (CH_3)_2NC_6H_4CHO = C_6H_4 \underset{\underset{CH_3}{|}}{\overset{CH=CH}{\underset{N-\!-\!-C=C=CHC_6H_4N(CH_3)_2}{\diagup}}} + H_2O$$

III

$$\text{III} + C_5H_{10}NH \cdot HI =$$

$$\left[C_6H_4 \underset{\underset{CH_3}{|}}{\overset{CH=CH}{\underset{N=\!=CCH=CHC_6H_4N(CH_3)_2}{\diagup}}} \right]^+ I^- + C_5H_{10}NH \qquad (115)$$

IV
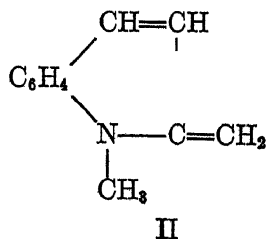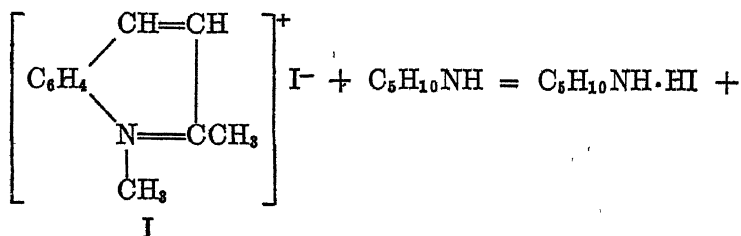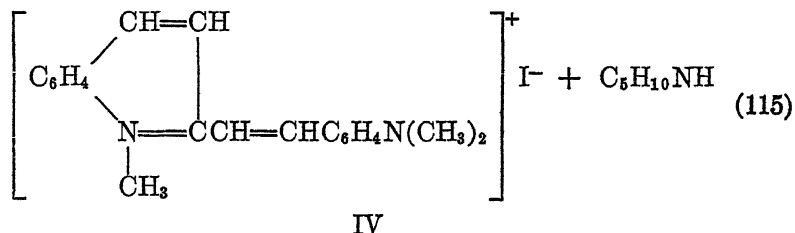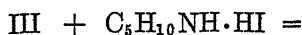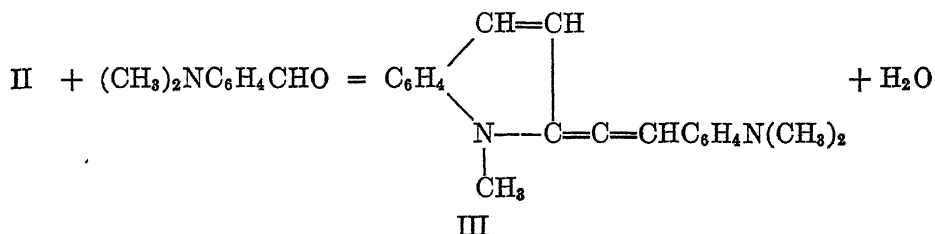
(b) Quinaldine alkiodides react with p-nitrosodimethylaniline in the manner of equation 116, but quinaldine itself (75, 463) does not.

$$\left[C_6H_4 \underset{\underset{CH_3}{|}}{\overset{CH=CH}{\underset{N=\!=CCH_3}{\diagup}}} \right]^+ I^- + (CH_3)_2NC_6H_4NO =$$

$$H_2O + \left[C_6H_4 \underset{\underset{CH_3}{|}}{\overset{CH=CH}{\underset{N=\!=CCH=NC_6H_4N(CH_3)_2}{\diagup}}} \right]^+ I^- \qquad (116)$$
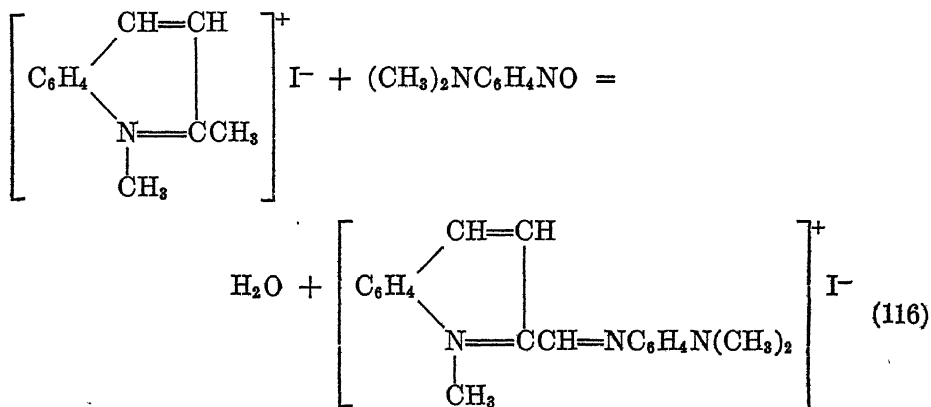
(c) Henze (421) has carried out reactions with quinoline N-oxide and quinaldine N-oxide

$$C_6H_4 \underset{\underset{O}{\downarrow}}{\overset{CH=CH}{\underset{N=\!=CCH_3}{\diagup}}}$$
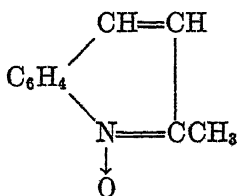
hoping that the reactivity would be enhanced by the positively charged nitrogen, just as it is with the quaternary quinaldinium salts. Definite conclusions cannot be drawn at the present time.

(d) Ammono aldehyde ethers and ammono esters or ammono aquo esters react

with quaternary salts containing a reactive methyl group.   It has thus been found
that the alkiodides of 2-methylbenzothiazole (V), quinaldine, lepidine, and re-
lated substances react not only with aquo aldehydes, but also with the ammono
dialdehyde ether, β-anilinoacrolein anil,

$$C_6H_5NHCH=CHCH=NC_6H_5 \rightleftarrows C_6H_5N=CHCH_2CH=NC_6H_5$$
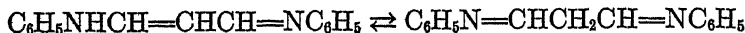
which may be considered to be a derivative of malondialdehyde (98).   Diphenyl-
formamidine (VI) is a diphenyl ester of ammonoformic acid (formamidine),
$HC(=NH)NH_2$, and resembles aquoformic acid or its esters in having aldehydic
characteristics.   Glutacondialdehyde dianil (VII) is an ammono dialdehyde
ether.

$$C_6H_5N=CHCH_2CH=CHCH=NC_6H_5 \rightleftarrows$$
$$C_6H_5NHCH=CHCH=CHCH=NC_6H_5$$

VII
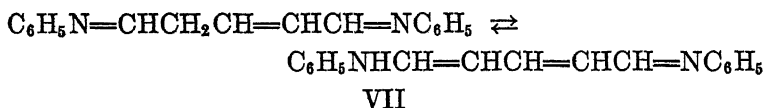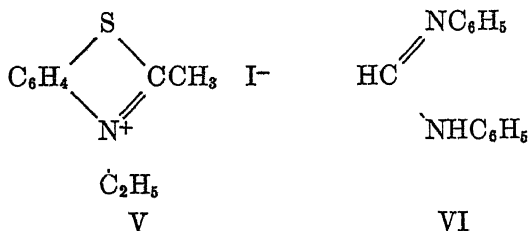
Diphenylformamidine ($n=0$), β-anilinoacrolein anil ($n=1$), and glutacondial-
dehyde dianil ($n=2$) may all be represented by the general formula VIII below,
and the reaction with a typical quaternary salt, 2-methylbenzothiazole ethiodide
(V), may be written in the following manner:
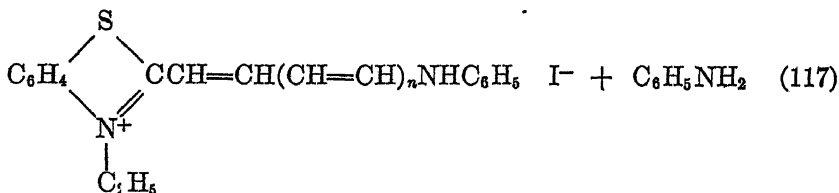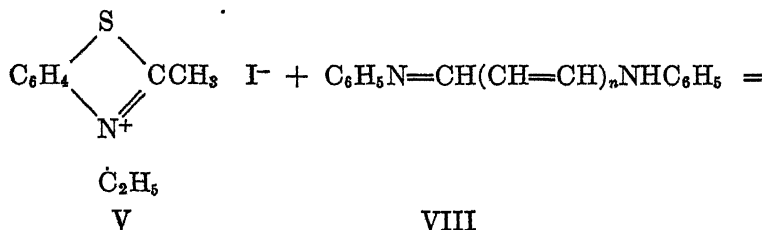
The anils are used as hydrochlorides, and when the condensation takes place in
acetic anhydride solution, the terminal —NHC_6H_5 becomes —N(COCH_3)C_6H_5.
The formation of these compounds affords a further example of the similarities of

the ammono aldehyde ethers (Schiff bases) and the aquo aldehydes (98, 655, 823a). The condensation products (IX) are useful in the preparation of cyanine dyes (see Section IV, N, 9, b, (1) to (3)).

6. The alkiodides of 2-alkylthio-, 2-alkylseleno-, and 2-aryloxy-quinolines

The alkiodides of 2-alkylthio- or 2-alkylseleno-quinolines may be prepared by heating 2-iodoquinoline alkiodides with a mercaptan or with an alkyl hydrogen selenide, respectively (91a). Together with the 2-aryloxyquinoline alkiodides, they have been of value in the preparation of some monomethine cyanine dyes that otherwise are not readily obtainable (Section IV, N, 9, b, (1)).

7. The alkiodides of 2- and 4-halogenated and 2- and 4-aminated quinolines

The reactivity of halogen in the 2- or 4-position of quinoline is increased by quaternary salt formation. 2-Iodoquinoline methiodide (394) thus reacts with boiling sodium hydroxide solution to form N-methylquinolone, and with alcoholic ammonia, dimethylamine, aniline, or phenylhydrazine to give 2-amino- or substituted 2-amino-quinoline methiodides (730b). Patents have recently been granted for the preparation of N-alkyl-2-quinolonimine derivatives by the action

$$C_6H_4 \diagup \overset{CH=CH}{\underset{N-C=NH}{\big|}} \diagdown \big| \atop R$$
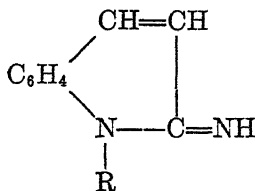
of ammonia or of amines on quaternary salts of 2-chloro- or 2-bromo-quinoline (666).

Brydówna (102a) prepared 4-iodoquinoline methiodide by heating 4-chloro-quinoline with methyl iodide, and found that it reacts readily with aniline, alcoholic ammonia, hydrazine, and phenylhydrazine to form 4-amino- or substituted 4-amino-quinoline methiodides. Alekseeva (8) heated 4-chloro-2-methylquinoline methiodide and aniline for 2 hr. at 120°C. and obtained the methiodide of 4-phenylamino-2-methylquinoline.

The 2- and 4-aminoquinoline alkiodides are often considered the hydro-iodides of 1-alkyl-2-(or 4-)quinolonimine (see formula above) (113b, 169). Both 2-aminoquinoline methiodide (730a) and 2-dimethylaminoquinoline methiodide (730) are converted to 1-methyl-2-quinolone

$$C_6H_4 \diagup \overset{CH=CH}{\underset{N-C=O}{\big|}} \diagdown \big| \atop CH_3$$
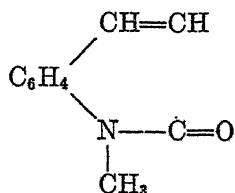
by boiling with an aqueous solution of sodium hydroxide. The methiodides of a cyclic ammono acid ester and of a cyclic ammono ester, respectively, have been

hydrolyzed to a cyclic ammono aquo ester and ammonia or dimethylamine. Since 2-aminoquinoline appears to be converted to 2-hydroxyquinoline with somewhat more difficulty (168), the hydrolyses under discussion have been accelerated by the positive charge on the nitrogen.

Advantage is taken of the reactivity of the nuclear halogen of 2- or 4-iodoquinoline or -pyridine alkiodides in the formation of cyanine dyes (see Section IV, N, 9, b, (1)).

8. Methylene bases from 2- and 4-alkylquinolines

The alkiodides of quinaldine, lepidine, and related compounds are converted by alkali to "methylene" bases, in the manner of the equations:

$$
\begin{bmatrix}
C_6H_4 \begin{smallmatrix} CH=CH \\ N=CCH_3 \\ CH_3 \end{smallmatrix}
\end{bmatrix}^+ I^-
\quad \underset{HI}{\overset{NaOH}{\rightleftarrows}} \quad
\begin{bmatrix}
C_6H_4 \begin{smallmatrix} CH=CH \\ N=CCH_3 \\ CH_3 \end{smallmatrix}
\end{bmatrix} OH^-
$$

I

II

$$
C_6H_4 \begin{smallmatrix} CH=CH \\ N-C=CH_2 \\ CH_3 \end{smallmatrix} \quad + H_2O \quad (118)
$$

III

Similarly,

$$
C_6H_4 \begin{smallmatrix} CH_3 \\ C=CH \\ N=CH \\ CH_3 \end{smallmatrix} I^- + NaOH =
C_6H_4 \begin{smallmatrix} CH_2 \\ C-CH \\ N-CH \\ CH_3 \end{smallmatrix} + H_2O + NaI
$$

IV

V
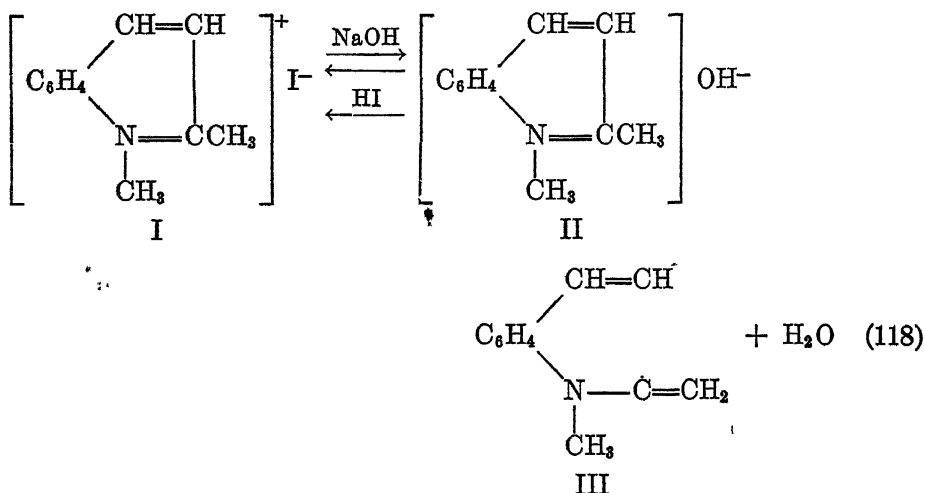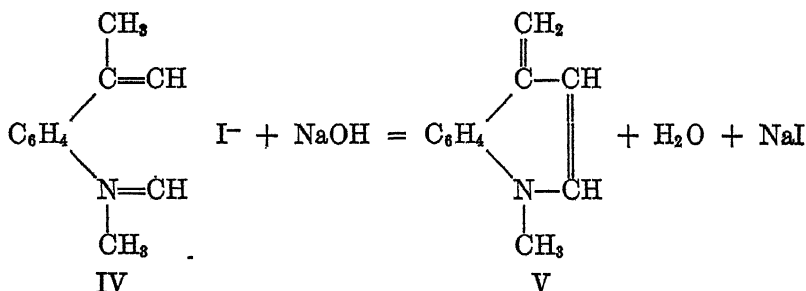
The mechanism of the formation of the methylene base (III or V) is not definitely known. Perhaps the pseudo base, with hydroxyl attached to either the 2- or the 4-carbon atom, is an intermediate which passes by loss of water into III or V.

It has been suggested that the first step in the reaction is the ionization of a hydrogen of the methyl group of the quaternary salt, a process that will be

favored by the positive charge on the nitrogen and also by an alkaline environment.

$$\underset{\text{VI}}{\underset{\underset{\overset{|}{\text{CH}_3}}{\overset{+}{\text{N}}=\dot{\text{C}}\text{CH}_3}}{\overset{\text{CH}=\text{CH}}{\underset{}{\text{C}_6\text{H}_4}}}} \qquad \underset{\text{VII}}{\underset{\underset{\overset{|}{\text{CH}_3}}{\overset{+}{\text{N}}=\dot{\text{C}}-\text{CH}_2{}^-}}{\overset{\text{CH}=\text{CH}}{\underset{}{\text{C}_6\text{H}_4}}}} \qquad \underset{\text{III}}{\underset{\underset{\overset{|}{\text{CH}_3}}{\text{N}-\dot{\text{C}}=\text{CH}_2}}{\overset{\text{CH}=\text{CH}}{\underset{}{\text{C}_6\text{H}_4}}}} \qquad (119)$$
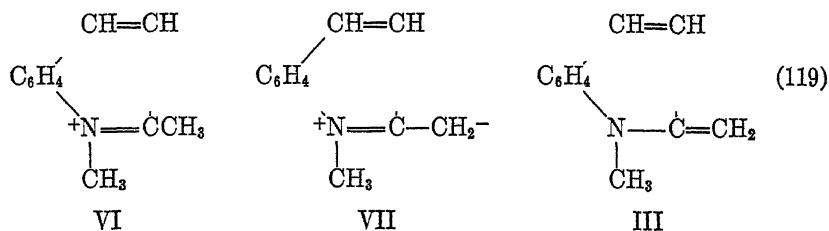
In this way there is formed the dipolar ion VII, which is in its non-polar form the methylene base itself (III). The two are doubtless in resonance. Some references to the methylene bases of the quinoline series are the following: 194, 505, 506, 507, 618, 720, 721a, 745, 746.

Decker (193a, 224a) has shown very clearly that there is an equilibrium between the methylene base (III) and the strong quaternary base (II) of equation 118. Non-aqueous and non-polar solvents extract the methylene base from water solution, while, conversely, water extracts the quaternary ammonium hydroxide (II) from the non-polar solvent.

The methylene bases are as a class difficult to isolate in an analytically pure condition and to keep because of their high chemical reactivity (cf. 618), which is comparable to that of the enolic form of an aquo ketone. 1-Methyl-2-methylene-1,2-dihydroquinoline (III) of equations 118 or 119 is the N-ether of the enamic or ammono enolic form of quinaldine, while 1-methyl-4-methylene-1,4-dihydroquinoline (V of equation 118) is a vinylogue.

Some of the reactions which are characteristic of the methylene bases are given below:

(a) The function of methylene bases as intermediates in the synthesis of styrylquinoline alkiodides and of the cyanine dyes is discussed elsewhere (see Sections IV, N, 5; IV, N, 9, b, (1)).

(b) Rosenhauer, Hofmann, and Unger (721a) prepared 1-methyl-2-methylene-1,2-dihydroquinoline (III) in the following manner: The quaternary salt formed by heating quinaldine and dimethyl sulfate was dissolved in a little water and dilute sodium hydroxide slowly added. The oily liquid separating was at once extracted with ether, and the latter then dried and concentrated in a vacuum desiccator to obtain yellow prisms (m.p. 71–72°C.) of the methylene base. This shortly turns reddish in air and resinifies, so an analysis must be carried out as rapidly as possible. If the ether extraction is delayed, or if the methylene base precipitates out in a solid form, it has a lower solubility, indicating that some polymerization has occured. Needless to say, most of the reactions of this compound have been carried out either with an ethereal solution (cf. 746) or with the unpurified material shortly after precipitation.

A more stable methylene base (VIII) has been prepared by Mills and Raper

(618) from the iodomethylate of 3,4-dimethyl-3,4-dihydrobenzo[f]quinoline, in accordance with the equation:

$$\text{VIII} \quad I^- \xrightarrow{\text{NaOH}} \quad + H_2O + NaI \quad (120)$$
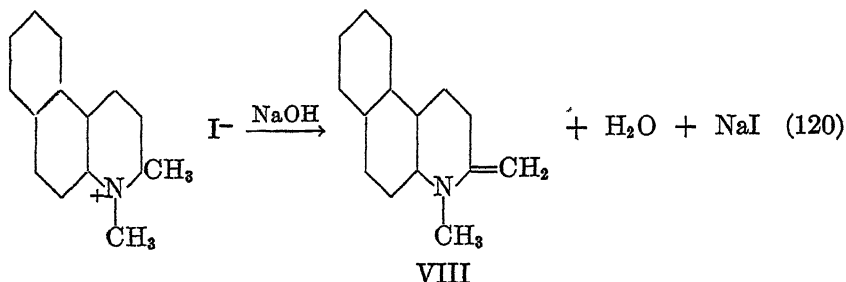
Mills (619a, 625), Robinson (13, 413, 714), Decker (194a), Sidgwick, Taylor, and Baker (760b), and others have adequately discussed the mechanism of the condensations undergone by the methylene bases.

(c) The methylene base from quinaldine ethiodide (IX), when heated for 0.5 hr. with benzyl iodide in benzene, gave a mixture of quinaldine ethiodide, dibenzylquinaldine ethiodide (X), and some isocyanine (619), in accordance with the equation below:

$$\text{IX} \qquad + \ C_6H_5CH_2I \ = \qquad \text{X} \qquad I^-$$

$$\text{X} + \text{IX} \qquad \qquad \qquad \qquad I^- + \qquad \qquad \text{XI}$$

$$\text{XI} + C_6H_5CH_2I \ = \qquad \qquad I^- \qquad (121)$$

$$\text{XII}$$
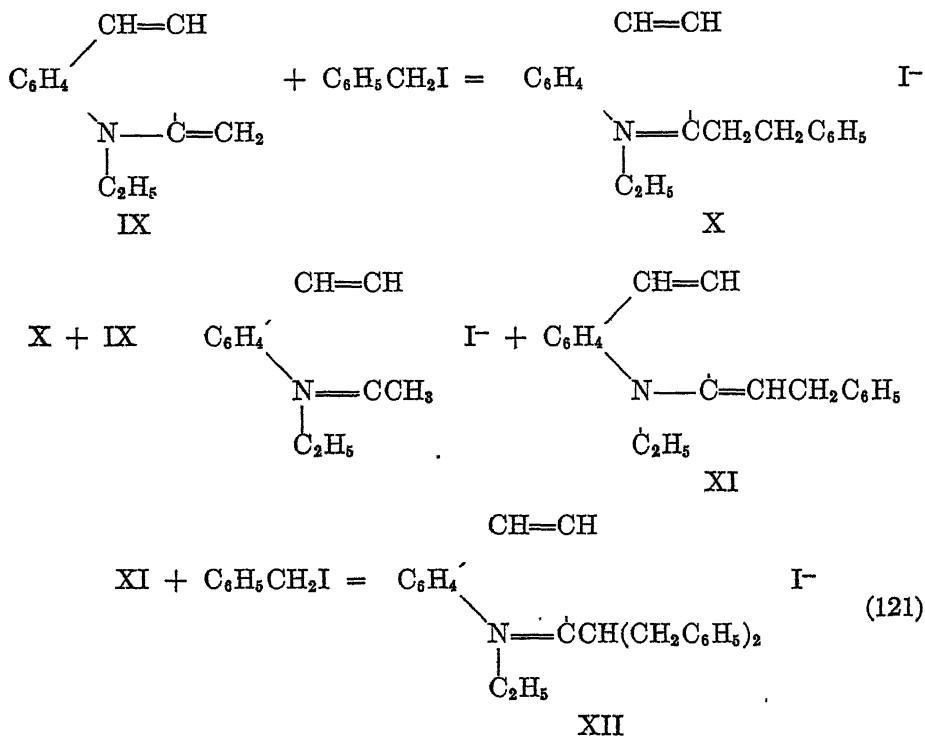
The first step of the reaction, IX → X, may be compared with the more rapid addition of hydrogen iodide to the methylene base to give a quaternary salt, as shown in the following equation:

$$\begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ N\!-\!C\!=\!CH_2 \\ | \\ R \end{array} \; + \; HI \; = \; \left[\begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ N\!=\!CCH_3 \\ | \\ R \end{array}\right]^{+} I^{-} \qquad (122)$$
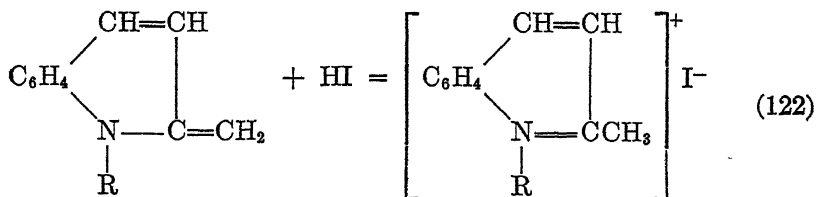
(*cf.* equation 118).

(*d*) 1-Methyl-2-methylene-1,2-dihydroquinoline and related compounds react readily with phenyl isothiocyanate or with phenyl isocyanate to form addition compounds, in the manner of the following equation (747):

$$\begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ N\!-\!C\!=\!CH_2 \\ | \\ CH_3 \end{array} \; + \; C_6H_5N\!=\!C\!=\!S \; \rightarrow \; \begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ N\!-\!C\!=\!CHCSNHC_6H_5 \\ | \\ CH_3 \end{array}$$

$$\xrightarrow[\text{etc.}]{\text{HI}} \quad \begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ {}^{+}N\!=\!CCH_2CSNHC_6H_5 \\ | \\ CH_3 \end{array} \quad I^{-} \quad (123)$$
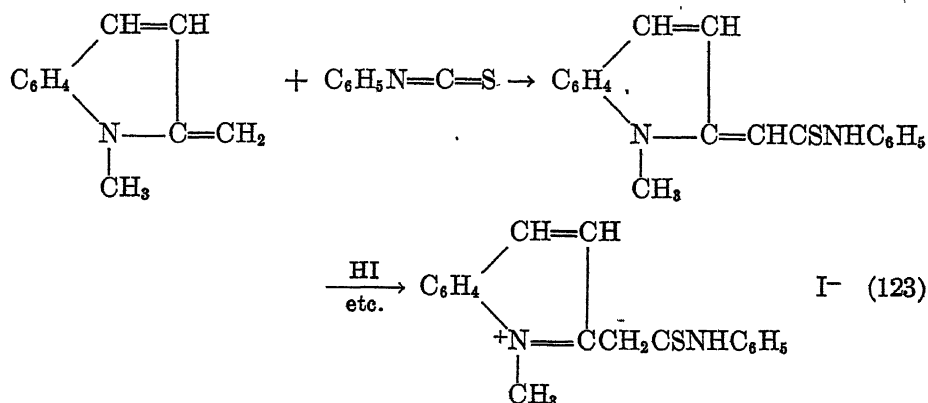
The methylene base has added to the $C\!=\!N$ linkage of phenyl isothiocyanate to form an intermediate, which halogen acid changes to the quaternary salt shown in the last formula above.

(*e*) Rosenhauer (718) treated 1-methyl-2-methylene-1,2-dihydroquinoline (XIII) in ether or benzene solution with bromine and obtained a yellow perbromide (XIV), which lost one atom of bromine when acetone was added, giving the highly reactive ω-bromoquinaldine methobromide (XV).

$$\begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ N\!-\!C\!=\!CH_2 \\ | \\ CH_3 \\ \text{XIII} \end{array} \xrightarrow{\text{Br}_2} \begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ {}^{+}N\!=\!CCH_2Br \\ | \\ CH_3 \\ \text{XIV} \end{array} Br_2^{-} \xrightarrow{(CH_3)_2CO}$$

$$\begin{array}{c} \overset{CH=CH}{C_6H_4 \diagup \quad \big|} \\ {}^{+}N\!=\!CCH_2Br \\ | \\ CH_3 \\ \text{XV} \end{array} \qquad Br^{-} \; \text{and} \; CH_2BrCOCH_3 \quad (124)$$
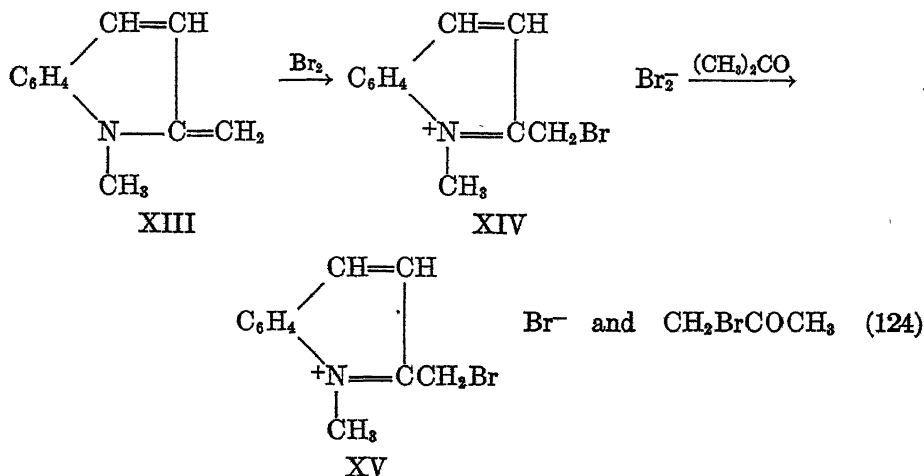
The bromine atom in the side chain of XV has an enhanced reactivity, at least toward amines and basic reagents, because of the effect of the positively charged nitrogen. Thus, when phenylhydrazine and XV are warmed for a short time on the water bath, the bromine is replaced in accordance with the following equation:

XV

XVI   XVII   (125)
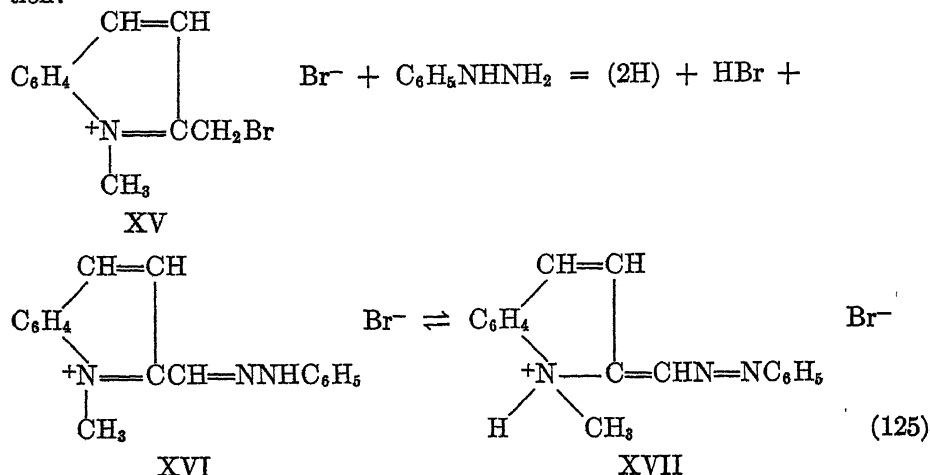
The expected reaction product has lost two hydrogens to form the dye, XVI or XVII.

(f) Armit and Robinson (13; cf. 413, 714) have added methyl iodide to an anhydro (methylene) base, in the manner of the equation:

(126)
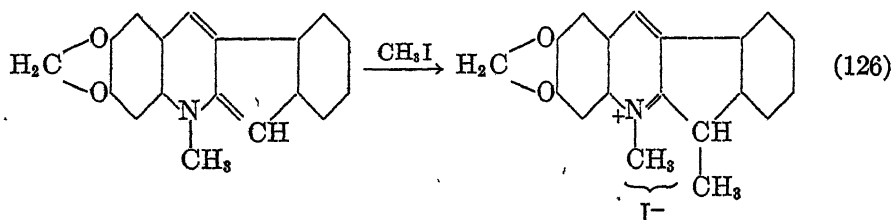
The resemblance to the reaction of Mills and Raper (Section (c) above; see reference 619) is evident.

(g) 2,4-Dinitrochlorobenzene and picryl chloride add to 1-methyl-2-methylene-1,2-dihydroquinoline to form addition compounds of the type of XVIII, which are considered to be carbenium salts (817) since hydrochloric acid is readily lost to give side-chain unsaturated substances similar to XIX.

XVIII

$$\xrightarrow{-HCl} \quad C_6H_4 \begin{array}{c} CH=CH \\ | \\ N\!-\!\!-C=CHC_6H_3(NO_2)_2 \\ | \\ CH_3 \end{array} \qquad (127)$$

XIX
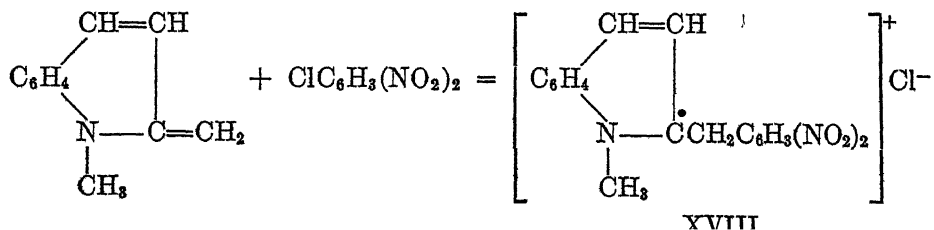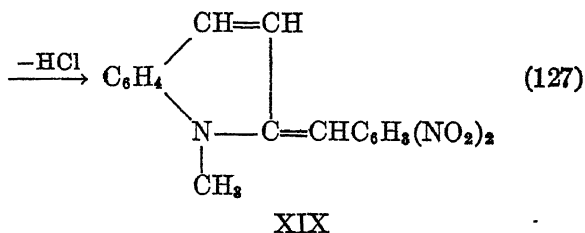
The positive charge is assumed to be localized on the 2-carbon atom of XVIII, but the reaction can be explained equally well by saying that it is on the nitrogen.

(*h*) 1-Methyl-2-methylene-1,2-dihydroquinoline, in resemblance to aceto-acetic ester and other enolizable ketones, reacts with diazonium salts in the sense of the following equation (495, 506, 507, 720):

$$C_6H_4 \begin{array}{c} CH=CH \\ | \\ N\!-\!\!-C=CH_2 \\ | \\ CH_3 \end{array} \quad + \; p\text{-}NO_2C_6H_4N_2Cl \; =$$

$$C_6H_4 \begin{array}{c} CH=CH \\ | \\ N\!-\!\!-C=CHN=NC_6H_4NO_2 \\ | \\ CH_3 \end{array} \qquad + \; HCl \quad (128)$$
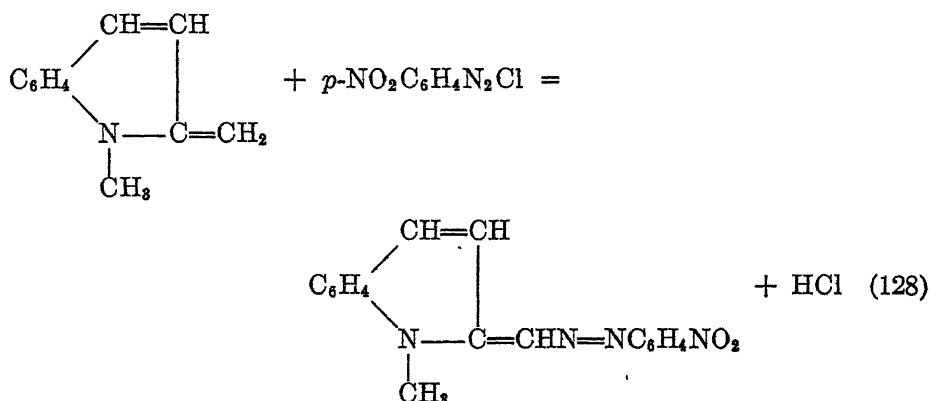
9. The cyanine dyes

Cyanine dyes have been prepared in very large numbers because of their action in sensitizing a photographic emulsion to wave lengths greater than the blue. It is far beyond the scope of this article to attempt an adequate description of the reactions involved in their preparation, or to make a complete survey of even limited portions of the field. Fortunately, the older work (before 1932) has been well covered by a review by Doja (258), and an excellent up-to-date general summary is to be found in Mees' new book (589).

In the formation of cyanines, advantage is almost always taken of the high reactivity of a methyl group in the α- or γ-position with respect to the nitrogen of quaternary salts of 2- and 4-methylpyridines, 2- and 4-methylquinolines, 2-methylbenzothiazole, and related compounds. The effect of the positively charged nitrogen in increasing the ketonic reactivity of the side-chain methyl group has been commented upon previously (see Sections II, I, 1 and IV, N, 5).

In the paragraphs that follow will be recognized close relatives of the aldol condensation (formation of apocyanines), the Michael reaction (2,4'- and 4,4'-cyanines), the Claisen ester condensation (formation of cyanines from quaternary salts of thio ethers or O-aryl ethers, formation of carbocyanines), the Claisen reaction (aldol condensation followed by loss of water; mono-, di-, and tri-carbocy-

anines, styrylquinolinium salts), and the alkylation (or acylation) of a ketone containing a reactive methylene group (2,2'-, 2,4'- and 4,4'-cyanines).

a. Cyanines with two nuclei directly connected: apocyanines

When a solution of quinoline ethiodide and potassium hydroxide in methyl alcohol is refluxed, two compounds are formed: xanthoapocyanine (I; yellow) and erythroapocyanine (II; red) (461, 615). The equation is given below:

$$(129)$$
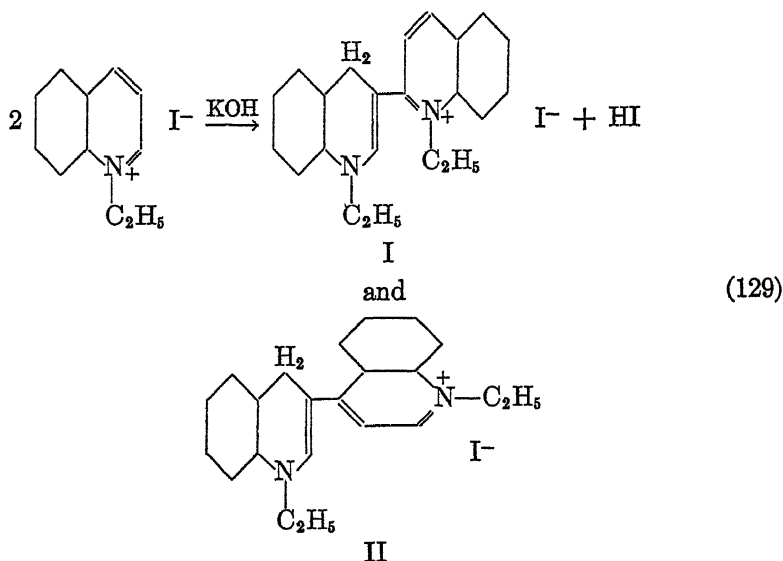
The apocyanines are resonance hybrids in the sense shown below:
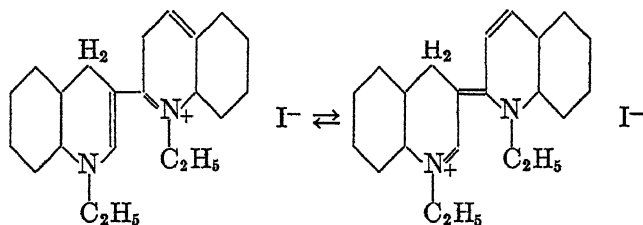
The formation of xanthoapocyanine may be regarded essentially as an aldol condensation of the activated cyclic aldehyde ether, quinoline ethiodide; comparison may be made with the related condensation of quinoline itself to dihydro-2,3'-diquinolyl (Section IV,K) under the influence of the strong base, sodium amide. The erythroapocyanine condensation concerns the related 4-position of one of the molecules of the quinolinium salt (615).

b. Cyanines with two heterocyclic nuclei separated by an unsaturated carbon chain

If —N=C— represents a heterocyclic nucleus, such as is found in pyridine, quinoline, benzoquinoline, or benzothiazole, one may represent the constitution of many cyanine dyes by the general formula:

$$^\lfloor\overset{+}{N}{=}\overset{|}{C}{-}(CH{=}CH)_n{-}CH{=}\overset{|}{C}{-}\overset{|}{N}{-} \rightleftarrows -\overset{|}{N}{-}\overset{|}{C}{=}CH{-}(CH{=}CH)_n{-}\overset{|}{C}{=}\overset{+}{N}^\rfloor$$
$$\overset{|}{\overset{.}{R}} \qquad\qquad \overset{|}{\overset{.}{R'}} \quad \overset{|}{\overset{.}{R}} \qquad\qquad \overset{|}{\overset{.}{R'}}$$

If lepidine or other compound having a reactive methyl in the γ-position is one of the reactants, the resulting dye will have one of the forms:

II

One nitrogen is always quaternary and the other tertiary, and the conjugation between the rings is unbroken. The color of the dyes and their stability is adequately explained by saying that the positive charge resonates between the two nitrogen atoms (96).

(1) The monomethine cyanines ($n=0$):

III   IV

V

The monomethine cyanines consist of two nitrogenous rings united in the α- or γ-positions through a methine (=CH—) bridge. The true cyanines (V) were first made by treating a mixture of the alkiodides of quinoline and of lepidine with an alkali (*cf.* 604a); the isocyanines (IV) (*cf.* 625a) were later prepared by the substitution of quinaldine alkiodides for the lepidine alkiodide. A typical dye (Ethyl red) is formed in accordance with the equation below (465a, 800):

$$\text{(structures)} \quad \text{I}^- \ + \ \text{(structures)} \quad \text{I}^- \ \xrightarrow{\text{KOH}}$$

$$\text{(structure)} \text{—CH=} \text{(structure)} \text{N—C}_2\text{H}_5 \quad \text{I}^- \ + \ \text{HI} \ + \ (2\text{H}) \qquad (130)$$

$$(\text{HI} \ + \ \text{KOH} \rightarrow \text{KI} \ + \ \text{H}_2\text{O})$$
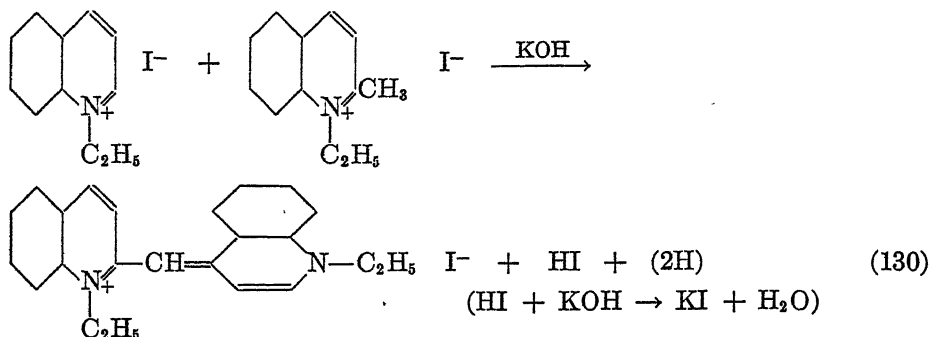
Quinaldine ethiodide (17.5 g.) and 33 g. (2 moles) of quinoline iodoethylate are dissolved in 1 liter of alcohol and treated with 33 cc. of 10 per cent alcoholic potassium hydroxide. After 2 days' standing at room temperatures, there had separated a mixture of crystals of Ethyl red and diethyl erythroapocyanine hydroiodide, which were obtained in pure condition by crystallization from alcohol (the latter is the more soluble). The yield of Ethyl red was 7.5 g., and of the erythroapocyanine, 14 g.

Decker and Kaufmann (219) say, "The formation of the cyanine dyes is due to the aldehydic function of the oxyhydro base (carbinol, or pseudo base) and the acid nature of the quinaldine methyl". In its barest details, the reaction can be expressed by the equation:

$$-\underset{\underset{R}{|}}{N}-\underset{\underset{R}{|}}{C}HOH + CH_3-\underset{\underset{R}{|}}{C}=\overset{+}{N}- \xrightarrow{\text{alkali}} -\underset{\underset{R}{|}}{N}-\underset{\underset{R}{|}}{C}H-CH_2-\underset{\underset{R}{|}}{C}=\overset{+}{N}-$$

$$\text{VI} \qquad\qquad \text{VII} \qquad\qquad\qquad\qquad \text{VIII}$$

$$\text{VIII} - 2H \longrightarrow -\underset{\underset{R}{|}}{N}-\underset{}{C}=CH-\underset{\underset{R}{|}}{C}=\overset{+}{N}-$$

$$\text{IX}$$

$$\left.\right\} \quad (131)$$
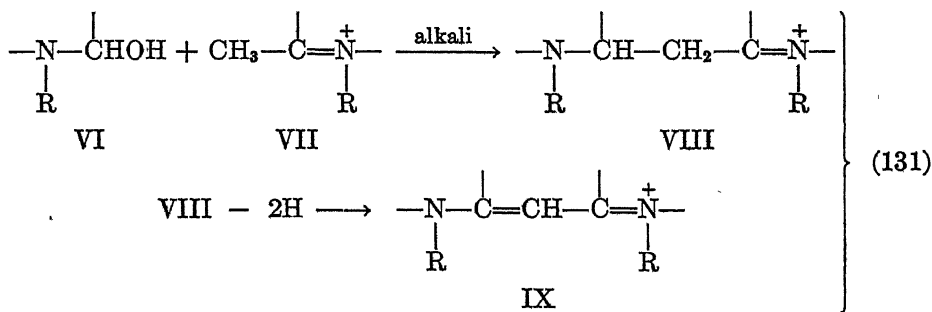
Unfortunately for this otherwise plausible theory, it was later shown that in this condensation, the quinoline alkiodide was attacked in the 4-position, rather than in the 2-, so that the pseudo base, which contains the grouping VI, cannot be an intermediate.

Vongerichten and Höfchen (800a) believe that the "isobase" or "methylene base" (XI) is the true carrier of the cyanine reaction, and Kaufmann and Vonderwahl (465) have suggested that this adds in the 1,4-position to the pseudo base of

the lepidinium salt, which they write in an open-chain form. An extension of their theory is presented below (*cf.* 715a):

$$
\begin{array}{c}
CH_3 \\
| \\
C=CH \\
C_6H_4 \quad | \\
+N=CH \\
| \\
C_2H_5
\end{array}
\quad \rightleftarrows \quad
\begin{array}{c}
CH_2^- \\
| \\
C=CH \\
C_6H_4 \quad | \\
+N=CH \\
| \\
C_2H_5
\end{array}
+ H^+ \quad \xrightarrow[-H_2O]{OH^-}
$$

(cation only)

$$
\begin{array}{c}
CH_2^- \\
| \\
C=CH \\
C_6H_4 \quad | \\
+N=CH \\
| \\
C_2H_5 \\
X
\end{array}
\quad \rightleftarrows \quad
\begin{array}{c}
CH_2 \\
\| \\
C-CH \\
C_6H_4 \quad \| \\
N-CH \\
| \\
C_2H_5 \\
XI
\end{array}
\qquad (132)
$$

$$
\begin{array}{c}
CH_2^- \\
| \\
C=CH \\
C_6H_4 \quad | \\
+N=CH \\
| \\
C_2H_5 \\
X
\end{array}
+
\begin{array}{c}
CH=CH \\
C_6H_4 \quad | \\
+N=CH \\
| \\
C_2H_5 \\
XII
\end{array}
\quad \rightarrow
$$

$$
\begin{array}{c}
C_2H_5 \\
| \\
+N=CH \\
C_6H_4 \quad | \\
C=CH \\
| \\
CH_2 \\
| \\
CH-CH \\
C_6H_4 \quad \| \\
N-CH \\
| \\
C_2H_5 \\
XIII
\end{array}
\quad \xrightarrow{-2H} \quad
\begin{array}{c}
C_2H_5 \\
| \\
+N=CH \\
C_6H_4 \quad | \\
C=CH \\
| \\
CH \\
\| \\
C-CH \\
C_6H_4 \quad | \\
N-CH \\
| \\
C_2H_5 \\
XIV
\end{array}
\qquad (133)
$$

Cation of 4,4'-diethyl
cyanine iodide

The positive charge will resonate between the two nitrogens of formula XIV.

Very little of the pseudo base is formed by treating quaternary quinolinium salts with alkali (17, 18). Perhaps it is more plausible to say that the cation (XII) of ethylquinolinium iodide or hydroxide is involved in the reaction rather than the pseudo base. The otherwise low aldehydic reactivity of quinoline itself has been greatly intensified by the positive charge on this ion. Ionization of a hydrogen from the ketonic methyl group of the quaternary lepidinium salt is facilitated by the charge on the nitrogen; there will result the dipolar ion (X), particularly in the presence of a base that can react with the proton. The nonpolar form of X is the familiar "methylene base" (XI) (cf. Section IV, N, 8), which is known to be formed when lepidine (or quinaldine) alkiodides are treated with alkali.

When the lepidinium (or a related) ion (X) is added to the 1,4-positions of the ethylquinolinium ion (XII), there results the leuco base (XIII), which is not isolated because organic matter present robs it of two hydrogens to give the cyanine (XIV). A counterpart of this reaction in the water system is the well-known addition of substances with reactive methyl or methylene groups to a double bond conjugated with carbonyl (the Michael reaction (603a)). In the following example, malonic ester adds to benzalacetophenone (XV) in the presence of piperidine to form ethyl (2-carbethoxy-3-phenyl-4-benzoyl)butyrate (XVI) (175a).

$$C_6H_5CH{=}CHC{=}O \quad + \quad CH_2(COOC_2H_5)_2 \qquad \underset{\text{reflux 72 hr.}}{\text{piperidine}}$$

$$\underset{\overset{|}{C_6H_5}}{}$$

XV

$$C_6H_5CHCH_2COC_6H_5$$
$$\underset{}{|}$$
$$CH(COOC_2H_5)_2$$

XVI
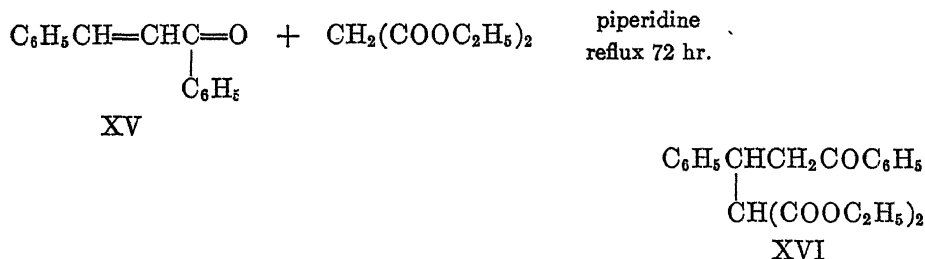
The Michael reaction is generally interpreted as involving the anion formed by the action of the basic catalyst upon the compound with the reactive methyl or methylene group. This anion probably adds in the 1,4-position to the conjugated system, $-CH{=}CH{-}\overset{|}{C}{=}O$, giving a product which rearranges to XVI upon hydrolysis. The related 1,4-addition of the Grignard reagent to a carbonyl conjugated with a double bond is well known from the work of Kohler (519b).

Monomethine cyanines are prepared more readily and in better yields by condensing a quaternary salt of an α- or γ-methylpyridine or -quinoline or of an α-methylbenzothiazole, etc., with an α- or γ-iodo-pyridine or -quinoline alkyl halide (394), in the presence, preferably, of potassium carbonate or of triethylamine (43b, 43c, 87d, 87f, 87i, 88, 92, 93, 94, 94b, 310, 313, 393, 395, 396a, 397, 402).

The preparation of a typical 2,2'- or pseudo-cyanine follows the equation:

$$
\left[\begin{array}{c} \text{CH}=\text{CH} \\ \text{C}_6\text{H}_4 \diagup \quad \Big| \\ \text{N}=\text{CI} \\ \Big| \\ \text{CH}_3 \end{array}\right]^+ \text{I}^- \;+\; \left[\begin{array}{c} \text{CH}=\text{CH} \\ \text{C}_6\text{H}_4 \diagup \quad \Big| \\ \text{N}=\text{CCH}_3 \\ \Big| \\ \text{CH}_3 \end{array}\right]^+ \text{I}^- \xrightarrow{-2\text{HI}}
$$

$$
\begin{array}{c} \text{CH}=\text{CH} \qquad\qquad \text{CH}=\text{CH} \\ \text{C}_6\text{H}_4 \diagup \quad \Big| \qquad\qquad\quad \Big| \quad \diagdown \text{C}_6\text{H}_4 \quad \text{I}^- \\ {}^+\text{N}=\text{C}-\text{CH}=\text{C}-\text{N} \\ \Big| \qquad\qquad\qquad \Big| \\ \text{CH}_3 \qquad\qquad\quad \text{CH}_3 \end{array} \qquad (134)
$$

XVII
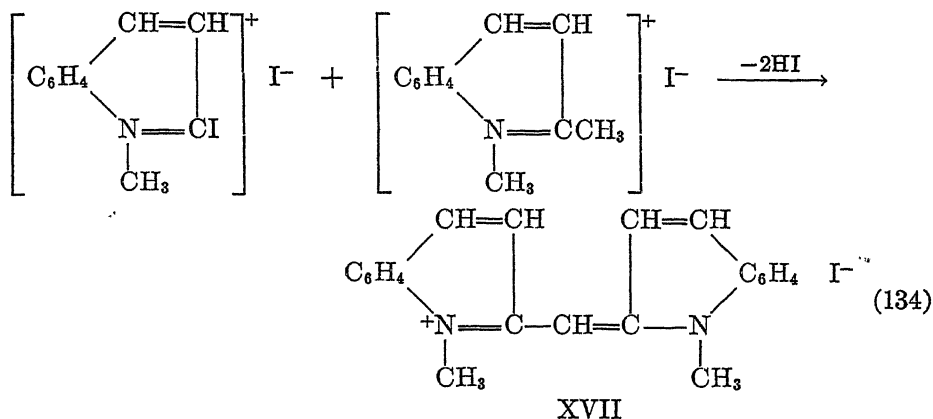
2-Iodoquinoline is a cyclic ammono acid iodide ester. The increased reactivity of the 2-halogen in the salt, 2-iodoquinoline methiodide, is undoubtedly not due to ionization of the iodine, for this will be greatly hindered by the positive charge on the cation. It seems more probable that the methylene base related to the quinaldine methiodide, perhaps in its dipolar resonant form (cf. X of equation 132), attacks the α-carbon atom directly. The cyanine is formed by loss of hydrogen iodide from this unstable intermediate. Another possibility is that the 2-iodoquinoline methiodide adds to the methylene base to form an addition compound that loses hydrogen iodide to give the cyanine.

Within recent years, the monomethine cyanines have been synthesized by methods which take advantage of the reactivity of an —SR, —SeR, or —OAryl group in compounds of the general types shown below (43c, 90a, 90b, 91a, 470b, 470c):

$$
\begin{array}{c} \text{CH}=\text{CH} \\ \text{C}_6\text{H}_4 \diagup \quad \Big| \qquad\quad \text{I}^- \\ \text{N}=\text{CSR}' \\ \Big| \\ \text{R} \end{array} \qquad\qquad \begin{array}{c} \text{CH}=\text{CH} \\ \text{C}_6\text{H}_4 \diagup \quad \Big| \qquad\quad \text{I}^- \\ \text{N}=\text{CSeR}' \\ \Big| \\ \text{R} \end{array}
$$

$$
\begin{array}{c} \text{CH}=\text{CH} \\ \text{C}_6\text{H}_4 \diagup \quad \Big| \qquad\quad \text{I}^- \\ =\text{CO Aryl} \\ \Big| \\ \text{R} \end{array}
$$
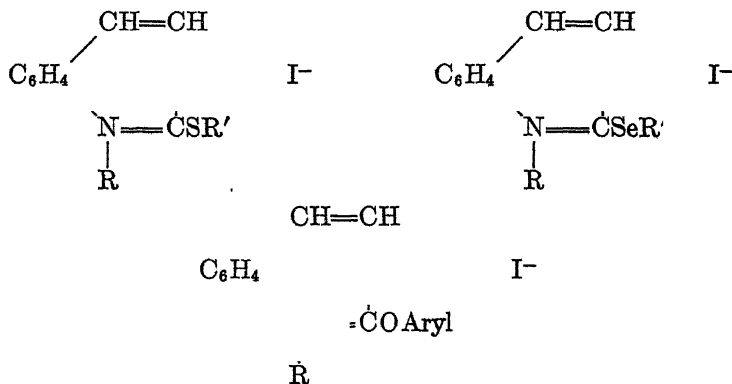
The thio and seleno ethers above are cyclic thio or seleno ammono esters, activated by quaternary salt formation. The formation from them of a cyanine dye is analogous in its first stage to the preparation of a β-diketone by the Claisen condensation, as in the following equation:

$$
\text{C}_6\text{H}_5\text{COOC}_2\text{H}_5 \;+\; \text{CH}_3\text{COC}_6\text{H}_5 \xrightarrow{\text{C}_2\text{H}_5\text{ONa}}
$$

$$
\text{C}_6\text{H}_5\text{COCH}_2\text{COC}_6\text{H}_5 \;+\; \text{C}_2\text{H}_5\text{OH} \qquad (135)
$$
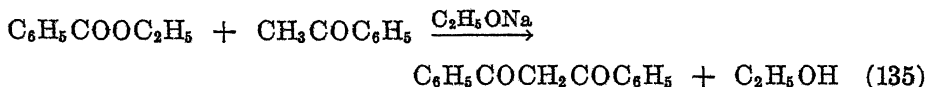
The cyanine is, of course, formed by loss of hydrogen iodide from the hypothetical intermediate.

Beilenson and Hamer (43c), following preliminary work of Kendall (470c, 470e), heated 2-thio-1-methyl-1,2-dihydroquinoline (XVIII) (a cyclic thio ammono ester) with methyl p-toluenesulfonate and obtained a quaternary salt (cation = XIX). When this was boiled for 3 min. with 2-methylbenzothiazole methiodide and anhydrous potassium carbonate, there was obtained an 84 per cent yield of crude 3,1'-dimethylthia-2'-cyanine iodide (XX). The same goal was reached more simply by fusing XVIII and 1-methylbenzothiazole with methyl p-toluene-sulfonate (150°C., 2 hr.) without the isolation of the quaternary salt.

$$\text{XIX} + \text{C}_6\text{H}_4 \overset{\text{S}}{\diamond} \text{CCH}_3 \quad \text{I}^- \rightarrow$$
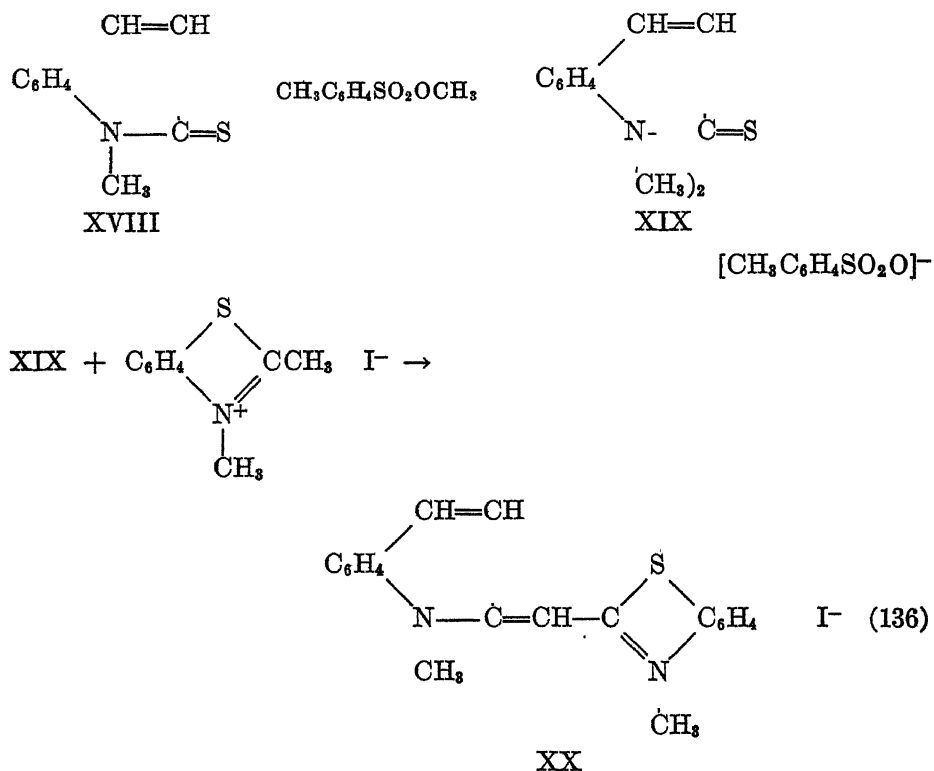
Attempts to prepare the same dye from 1-methyl-2-keto-1,2-dihydroquinoline (N-methyl-α-quinolone)
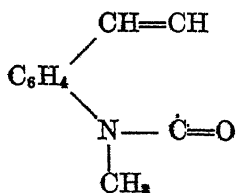
under the same conditions failed, doubtless because the quinolone does not form a quaternary salt, and is therefore not sufficiently reactive. The formation of the

thiacyanine of equation 136 resembles a Claisen condensation as well as a Claisen reaction (aldol condensation followed by loss of water).

(2) *Carbocyanines* $(n=1)$: The best-known carbocyanine is pinacyanole (I), a panchromatic sensitizer. It may be made by refluxing quinaldine ethiodide with formaldehyde, paraformaldehyde, ethyl orthoformate (this is recommended), or even with iodoform (722) in the presence of a base, such as pyridine (301, 392a, 555, 613, 643a (cryptocyanines), 644, 658, 722; for mechanism see 392, 505, 505a, 613). The reaction is expressed by the equation:

$$2C_6H_4 \diagup_{\substack{\\ \overset{+}{N} \stackrel{.}{=\!=} \overset{.}{C}-CH_3 \\ | \\ C_2H_5}}^{CH=CH} \quad I^- + HC(OC_2H_5)_3$$

$$C_6H_4 \diagup_{\substack{\\ \overset{+}{N} =\!=CCH=CHCH=C \\ | \\ C_2H_5}}^{CH=CH} \qquad \diagdown_{\substack{CH=CH \\ \\ N \\ | \\ C_2H_5}}^{} C_6H_4 \quad I^- + 2C_2H_5OH + HI \quad (137)$$
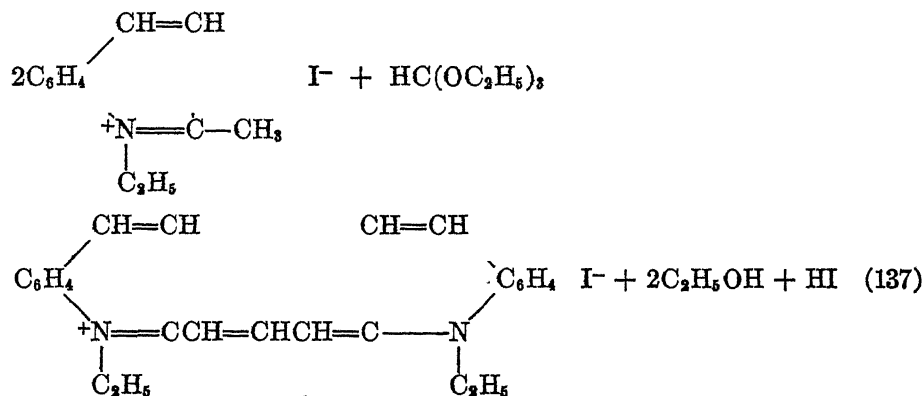
The hydrogen iodide of course reacts with the base used as a condensing agent, while the positive charge resonates between the two nitrogens (*cf.* 92, 94a, 96, 548b, 610b, 625b, 644a).

Mills and Hamer (613) believe that formaldehyde first condenses with quinaldine methiodide in the manner of the equation:

$$\overset{|}{C}CH_3 + HCHO + CH_3\overset{|}{C} \quad \longrightarrow$$

$$\overset{|}{C}CH_2CH_2CH_2\overset{|}{C} \qquad (137a)$$

(Diethiodide of methylene diquinaldine)
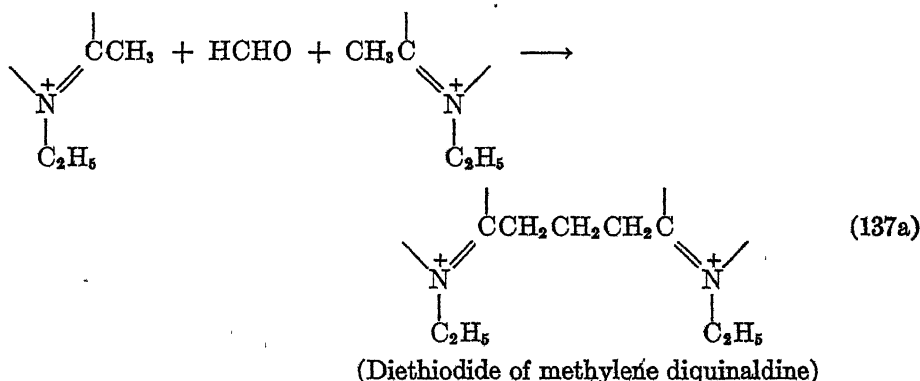
Related reactions between formaldehyde and acetoacetic ester (697b) or malonic ester (477a) in the presence of piperidine or diethylamine as a catalyst give methylene bisacetoacetic ester or methylene bismalonic ester, respectively. The trimethylene intermediate of formula 137a loses a proton in the alkaline medium in which the reaction takes place and is oxidized to give the cyanine dye, pinacyanol.

Miss Hamer succeeded in preparing the dimethiodide of methylene diquinaldine by the action of formaldehyde on quinaldine methiodide in the presence of piperidine (392); the diethiodide was prepared by a somewhat more roundabout method. When either of these compounds was heated with alkali under the conditions of the carbocyanine condensation, less than 4 per cent of the latter was formed. The yield was increased tenfold by the addition of an alkiodide of quinoline, though much less effect was observed when a quaternary salt of quinaldine was used. Perhaps this is a case of positive-ion catalysis (see Section VI, A, 1 and reference 740a for related work).

The use of esters of orthoacetic acid, orthobenzoic acid and their homologues makes it possible to synthesize carbocyanines with a substituent in the three-carbon-atom bridge (87b, 97). Ammono aquo esters (imino esters, imino "ethers") of the general formula, $RC(=NH)OR'$, in which R and R' are alkyl, aralkyl, or aryl residues, and certain acid anhydrides (470f) may also serve as intermediates in the formation of cyanines (470a). The esters are made by the addition of alcohol to a nitrile in the presence of hydrochloric acid (compare the formation of diethyl malonate by heating cyanoacetic acid with alcohol and sulfuric acid).

In the action of N,N'-diphenylformamidine on a quaternary salt of quinaldine or a similar compound with reactive methyl, a β- phenylaminovinyl derivative is first formed in accordance with equation 117. Further action with another molecule of the same or of a different quaternary salt with reactive methyl will give a carbocyanine dye, as shown below (43b, 87c, 90c, 94a, 98, 470d, 470g, 470h, 643a, 644a, 655):
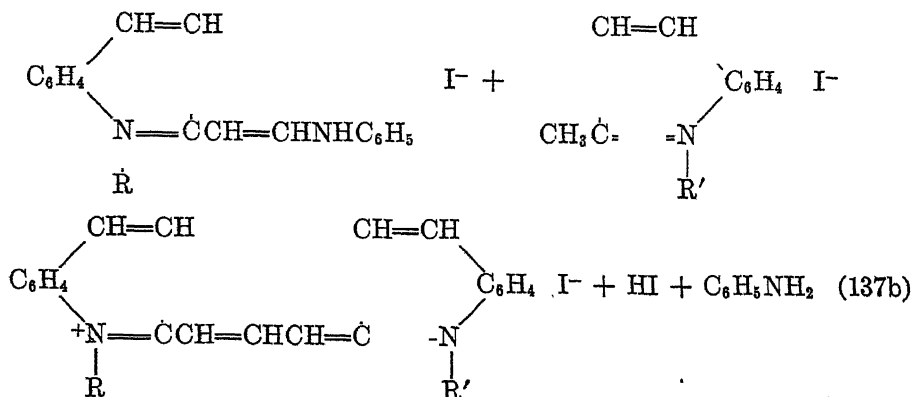
Insofar as the side chain is concerned, the quinaldine derivative on the upper left-hand side of the equation is a monophenyl ether of an ename, or ammono enol, $RCH=CHNH_2$. In its tautomeric form, $RCH_2CH=NC_6H_5$, it is an ammono aldehyde ether. The replacement of $-NHC_6H_5$ in the one case or of $=NC_6H_5$ in the other case is analogous to the replacement of the oxygen of an enolizable aldehyde with the residue of a compound with reactive methylene. It will be noted that here, as in most cyanine dye syntheses, the conjugated chain separating the two nuclei is formed by elimination of hydrogen iodide from a

possible intermediate, resulting in a considerable stabilization of the molecule by the added resonance.

Lepidine alkiodides can of course be used in the preparation of 4,4'-cyanines by methods that are similar to the above (see earlier references on carbocyanines and also 392a and 645). For the preparation of the related neocyanines, see reference 396.

(*3*) *Dicarbocyanines* (*n = 2*) *and tricarbocyanines* (*n = 3*): Beattie, Heilbron, and Irving (41b) prepared a dicarbocyanine dye by heating α-bromo- and β-anilinoacryaldehyde anil, $C_6H_5NHCH{=}CBrCH{=}NC_6H_5$, with quinaldine ethiodide in a pyridine solution that contained some piperidine. Piggott and Rodd (655) and Brooker (98) have recently prepared many dicarbocyanines with the use of β-anilinoacrolein anil itself. It will be noted that this compound is, in its tautomeric form, the dianil of malondialdehyde, that is to say, an ammono dialdehyde diether.

Tricarbocyanines are obtained by heating a quaternary salt of quinaldine, lepidine, or a related substance, with the dianil of glutacondialdehyde (87e, 90, 91, 312, 401a, 823a) in the manner of the equation:

$$CH{=}CH$$
$$C_6H_4 \diagdown$$
$$\diagup$$
$$N{=\!=}\dot{C}CH_3$$
$$|$$
$$R$$

$$I^- \; + \; C_6H_5NHCH{=}CHCH{=}CHCH{=}NC_6H_5 \; +$$

$$CH{=}CH$$
$$\diagdown C_6H_4 \; I^-$$
$$CH_3\dot{C} \quad {=}N \diagup$$
$$|$$
$$R$$

$$CH{=}CH \qquad\qquad\qquad CH{=}CH$$
$$C_6H_4 \diagup \qquad\qquad\qquad \diagdown C_6H_4 \; I^-$$
$${}^+N{=\!=}\dot{C}CH{=}CHCH{=}CHCH{=}CHCH{=} \quad N \diagup$$
$$| \qquad\qquad\qquad\qquad\qquad\qquad |$$
$$R \qquad\qquad\qquad\qquad\qquad\qquad R$$

$$+ \; HI \; + \; 2C_6H_5NH_2$$
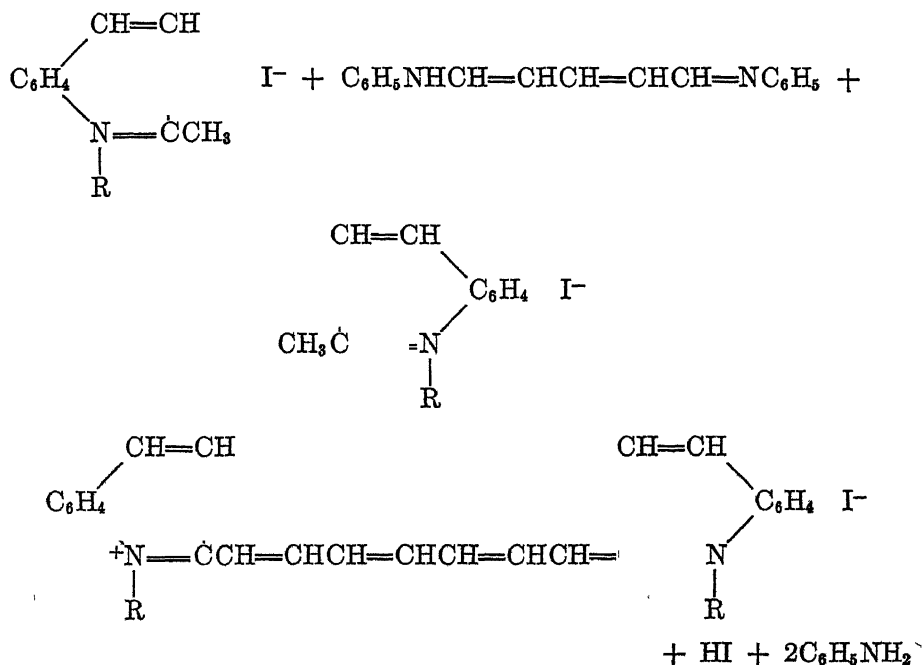
The relationship of glutacondialdehyde dianil to the ammonia system has been given in Section IV, N, 5, d; its preparation has been described in Section II, C, (a). The quaternary salt formed by adding 2-iodoquinoline to pyridine may also be used as a source of glutacondialdehyde (87 g.). Polymethine dyes have been made by the ammonolysis of an unsymmetrical dye of the pyrylium series by ammonia or a primary amine (654a).

c. Styrylquinolinium salts

Styrylquinolinium salts, which have some action as photographic sensitizers, have been dealt with in an earlier section (IV, N, 5, (a)).

d. Azacyanines

2,2'-Pyridylaminoquinoline ethiodide (I) is formed by short boiling of 2-iodoquinoline ethiodide with an excess of 2-aminopyridine in absolute alcohol (316), the reaction proceeding in accordance with the equation:

$$
\underset{\underset{\dot{C}_2H_5}{\underset{|}{\dot{C}I}}}{C_6H_4}\!\!\diagup^{CH=CH}\quad I^- \;+\; NH_2C\!\!\diagdown_{N}^{CH \diagup CH \diagdown CH}\diagdown_{CH}^{CH} \longrightarrow
$$

$$
C_6H_4\!\!\diagup^{CH=CH}\!\!\diagdown_{\underset{\dot{C}_2H_5}{\overset{+}{N}}=C-NH-C}\!\!\diagdown_{N}^{CH \diagup CH \diagdown CH}\diagdown_{CH}^{CH} \quad I^- \;+\; HI \qquad (137c)
$$
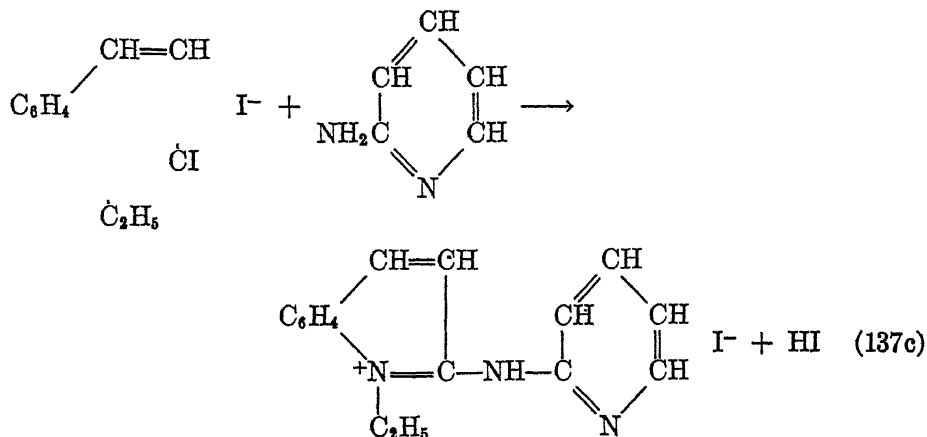
The pyridylaminoquinoline ethiodide (I) is boiled with sodium carbonate solution, and the resulting unsaturated compound then converted to a quaternary salt, the azacyanine (II), by heating with methyl iodide.

$$
C_6H_4\!\!\diagup^{CH=CH}\!\!\diagdown_{\underset{\dot{C}_2H_5}{N}-\dot{C}=N-C}\!\!\diagdown_{\overset{+}{N}}^{CH \diagup CH \diagdown CH}\diagdown_{\dot{C}H}^{CH} \quad I^-
$$
$$
\dot{C}H_3
$$

II
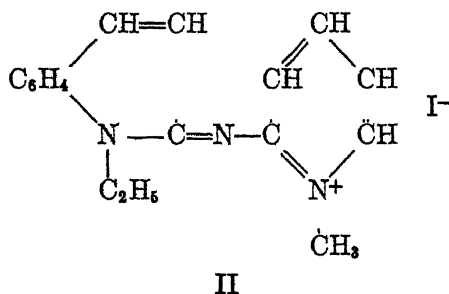
Here again is an illustration of the ease with which the nuclear halogen in 2-iodoquinoline ethiodide may be replaced.

e. Anhydronium bases

The anhydronium bases corresponding to a number of cyanine dyes have been made, either by heating the dye in a high vacuum (467) or with dimethylaniline (96, 398, 752a) or by synthesis (610a).

O. QUINOLINECARBOXYLIC ACIDS

Pyridine-2-acetic acid (Section II, N) resembles β-keto acids in that it loses carbon dioxide readily when gently heated. The related quinoline-2-acetic acid is on the other hand much more stable, as it melts at 274–275°C. (273, 471). It is interesting that quinoline-2-carboxylic acid (quinaldic acid) melts at 156°C. when anhydrous, and quinoline-2-propionic acid melts at 122–123°C. (273), so that quinoline-2-acetic acid is out of line in this regard also.

Decarboxylation of quinoline-2,4-dicarboxylic acid in boiling nitrobenzene for 10 min. gives a 90 per cent yield of quinoline-4-carboxylic acid (cinchoninic acid) (711; cf. 819c). The removal of carbon dioxide can also be effected by heating alone at 240°C. (686; cf. 81c) or in phenol at its boiling point (502).

Quinoline-2,3-dicarboxylic acid (acridinic acid) loses carbon dioxide at 120–130°C. to form quinoline-3-carboxylic acid (377), showing that the —C=N— group affects the carboxyl directly attached to it. The literature does not permit a decision as to the relative stability of quinoline-3- and 4-carboxylic acids.

(For the mechanism of the decarboxylation of quinaldinic acid, see reference 264 and Section II,N.)

V. ISOQUINOLINE

Isoquinoline (II) resembles quinoline (IV) in most respects. The properties of the two, while generally similar, are not identical, because the former is a cyclic Schiff base (ammono aldehyde ether) derived from a substituted benzaldehyde (I), while the latter is a cyclic Schiff base related to o-aminocinnamaldehyde (III).

$$C_6H_4\Big\langle{}^{CH=CHNH_2}_{CHO} \quad \xrightarrow{-H_2O} \quad C_6H_4\Big\langle{}^{CH=CH}_{CH=N} \quad \text{or} \quad (138)$$

I   II

$$C_6H_4\Big\langle{}^{CH=CHCHO}_{NH_2}$$

III   IV
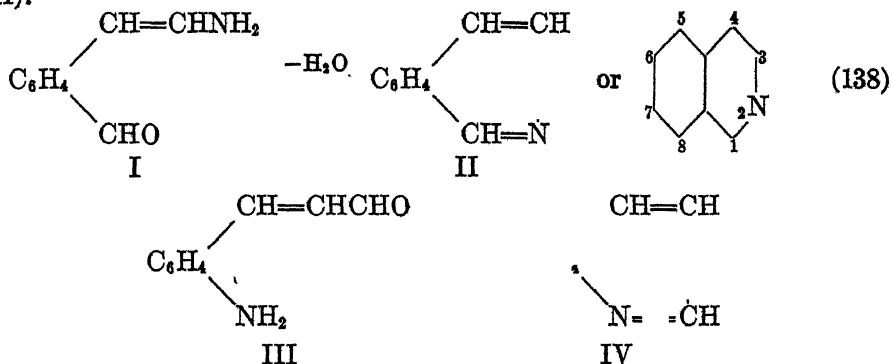
The differences between quinoline and isoquinoline are reflections of the dissimilarity of benzaldehyde and cinnamaldehyde.

More exactly, one should perhaps regard isoquinoline as formed by the ammonolysis of the dialdehyde (V):

$$C_6H_4\Big\langle{}^{CH_2CHO}_{CHO} \quad C_6H_4\Big\langle{}^{CH=CHOH}_{CHO} \quad \xrightarrow{+NH_3} \quad C_6H_4\Big\langle{}^{CH=CH}_{CH=N} \quad (139)$$

V   VI   II
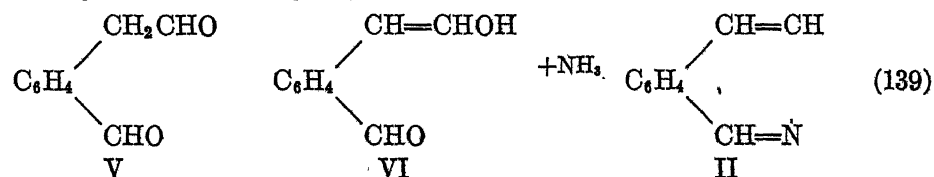
A similar situation exists with regard to pyridine, but here, as there, it is considered better to adopt the simpler but generally adequate viewpoint that isoquinoline is a cyclic ammono aldehyde ether. On this basis, it follows that 1-methylisoquinoline and 1-phenylisoquinoline are cyclic ammono ketone ethers, that 1-hydroxyisoquinoline (isocarbostyryl) is a cyclic ammono aquo acid ester, that 1-chloroiosoquinoline is a cyclic ammono acid chloride ester, and that 1-aminoisoquinoline is a cyclic ammono acid ester. It will be seen on inspection of formula II of equation 138 that the 1-carbon and attached groups will be unique in that no other position in the ring will have their function. Thus, while the alkyl groups of 2- and 4-methylquinolines are similar chemically, the same situation cannot exist in the isoquinoline series. Although ring resonance might make the 1- and 3-methyls equivalent, in that, at separate intervals, each will be attached to a —C==N— group, this is not the case, since the 3-methyl has been shown to be inactive (621).

A. SYNTHESES OF ISOQUINOLINE

The discussion of the syntheses of isoquinoline and its derivatives will be abbreviated, because of the existence of a previous review covering this field (585). A few of the methods are listed below.

1. Bischler–Napieralski synthesis

Acyl derivatives of β-phenethylamine, when heated with phosphorus pentoxide or certain other dehydrating agents, give 1-substituted 3,4-dihydroisoquinolines, in accordance with the scheme:

$$ \text{(140)} $$

VII   VIII
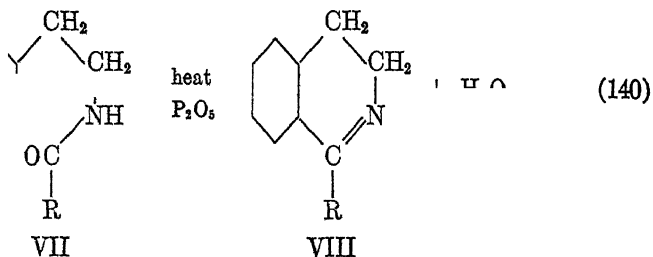
Isoquinoline itself is not advantageously made in this manner, although many substitution products are, since they may be obtained by oxidizing or dehydrogenating the intermediate 3,4-dihydride (VIII; 195, 227, 228, 688, 768, 770).

The N-acyl derivatives of β-phenethylamine (VII) are substituted acid amides and therefore ammono aquo acid esters (see Section I, G). For this reason, the "ketonic reactivity" of the carbonyl group should be greater than in an acid amide (ammono aquo acid) and perhaps somewhat less than in a neutral ester. The ring closure can be said to follow the general pattern of the Skraup and Döbner–von Miller syntheses (Sections IV, A, 3 and 4) and to result from a reaction between a carbonyl of a side chain and a ring hydrogen. The synthesis of phenanthridines from acyl derivatives of o-aminobiphenyl is closely related (see forthcoming review).

It is not known whether an intermediate addition compound (IX) similar to the aldol base of Döbner and von Miller (Section IV, A, 4) is formed

$$C_6H_4 \diagup \begin{array}{c} CH_2-CH_2 \\ \\ C-NH \\ HO \diagup \diagdown R \end{array}$$

IX
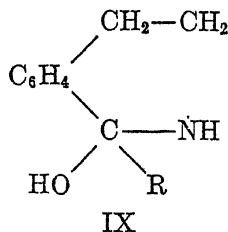
or whether ring closure is the result of loss of water between the imidol modification of VII

$$HO-C \begin{array}{c} | \\ N \\ \diagup\diagup \\ \\ | \\ R \end{array}$$
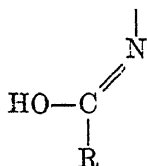
and a ring hydrogen; if this is the case, there is a relationship to the conversion of o-benzoylbenzoic acid to anthraquinone or to the reaction of Groggins (381) below:

$$C_6H_6 + CH_3COOH + 2AlCl_3 =$$
$$C_6H_5COCH_3 + AlOCl + 2HCl + AlCl_3 \quad (141)$$

2. Aminoacetal synthesis

Arylidene amino acetals, when warmed with concentrated sulfuric acid, or with sulfuric and arsenic acids, give isoquinoline or substituted isoquinolines, as shown by the representative equation below (693, 732; cf. 775):

$$C_6H_5CHO + NH_2CH_2CH(OC_2H_5)_2 \rightarrow C_6H_5CH=NCH_2CH(OC_2H_5)_2 + H_2O$$
I

$$(142)$$

I   II
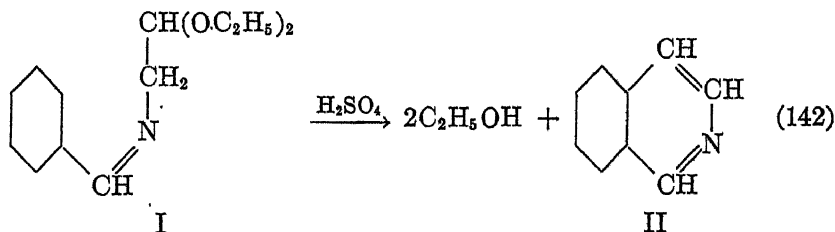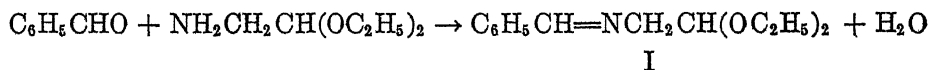
This method is of limited application, although recently it has been utilized to prepare a number of bromoisoquinolines, which have been converted successively to the cyanides and to the carboxylic acids (799).

The first step in the reaction is the familiar ammonolysis of an aquo aldehyde to a substituted ammono aldehyde ether, or Schiff base (I). The ring closure is brought about by attack of the terminal —CH(COOC$_2$H$_5$) of the side chain,

which is aldehydic in character, on a hydrogen in the ortho position in the benzene ring. It has been shown by Staub (775) that cyclization occurs most readily when this condition is fulfilled, and we find numerous other examples among the quinoline syntheses previously discussed (see Section IV, A). The formation of triphenylmethane derivatives by the action of dialkyl-anilines or -phenols upon aromatic aldehydes may be regarded as a related type of reaction.

3. The Pictet–Gams synthesis

Acylated aminomethylphenyl carbinols of the type formula, $C_6H_5CH(OH)$-CH_2NHCOR (100, 687), or the corresponding aminophenylcarbinol ethers (723, 724) give isoquinolines directly when heated with phosphorus pentoxide in toluene or in xylene. The equations are the following:

$$C_6H_5COCH_3 \xrightarrow[NaOC_2H_5]{C_5H_{11}ONO} C_6H_5COCH{=}NOH \xrightarrow[HCl]{SnCl_2}$$

$$C_6H_5COCH_2NH_2 \cdot HCl \xrightarrow{RCOCl} C_6H_5COCH_2NHCOR \xrightarrow[\text{absolute alcohol}]{\text{Na amalgam}}$$

$$C_6H_5CH(OH)NHCOR \xrightarrow[\text{heat}]{P_2O_5} C_6H_4 \begin{array}{c} CH{=}CH \\ | \quad\quad | \\ C{=}N \\ | \\ R \end{array} \quad (143)$$

$$C_6H_5CHO \xrightarrow[\text{alkali}]{CH_3NO_2} C_6H_5CH{=}CHNO_2 \xrightarrow{CH_3ONa}$$

$$C_6H_5CH(OCH_3)CH_2NO_2 \xrightarrow{(6H)} C_6H_5CH(OCH_3)CH_2NH_2 \xrightarrow{RCOCl}$$

$$C_6H_5CH(OCH_3)CH_2NHCOR \xrightarrow[\text{heat}]{P_2O_5} C_6H_4 \begin{array}{c} CH{=}CH \\ | \quad\quad | \\ C{=}N \\ | \\ R \end{array} \quad (144)$$
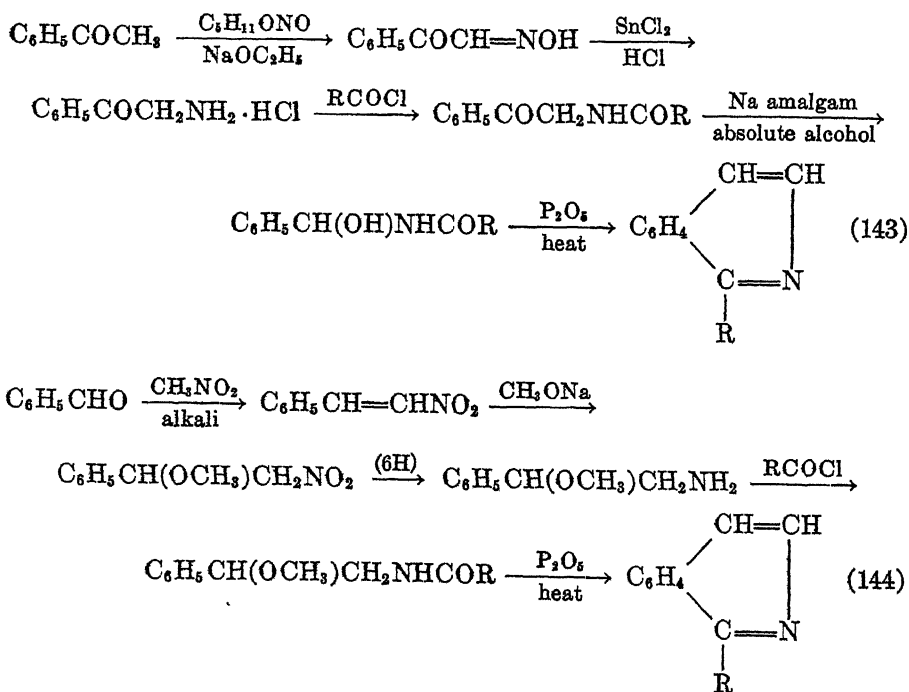
The interpretation of the reaction is essentially the same as given for the Bischler–Napieralski synthesis.

Krabbe and coworkers (535–539) have shown that the N-acylvinylamines of the type $R_2C{=}C(R')NHCOR''$ (a specific example is $C_6H_5CH{=}CHNHCOR$) are intermediates in this synthesis. They represent the first step in the conversion of the acylated aminophenylcarbinol (see equation 143) or of the methyl ether (see equation 144) to the isoquinoline derivative. It is recommended (539) that the carbinol be dehydrated first to the vinyl compound by means of an alkaline dehydrating agent, say RMgX, and the ring then closed in the usual manner with phosphorus pentoxide. Otherwise, oxazolines may be formed as by-products.

4. Isocarbostyryl syntheses

Hydroxyisoquinolines are·prepared by heating isocoumarins with ammonia, just as the pyridones or hydroxypyridines are made by the ammonolysis of pyrones. Thus, 1-hydroxyisoquinoline, or isocarbostyryl, is formed in almost quantitative yield by heating isocoumarin with alcoholic ammonia at 120–130°C., in accordance with the equation (105):

$$\underset{C_6H_4}{\overset{CH=CH}{\diagdown}} \quad + NH_3 = \underset{C_6H_4}{\overset{CH=CH}{\diagdown}} \quad \underset{C_6H_4}{\overset{CH=CH}{\diagdown}} \quad + H_2O \quad (145)$$

$$\overset{\cdot}{C}O—\overset{\cdot}{O} \qquad CO—\overset{\cdot}{N}H \qquad =\overset{\cdot}{N}$$
$$\overset{\cdot}{O}H$$

II
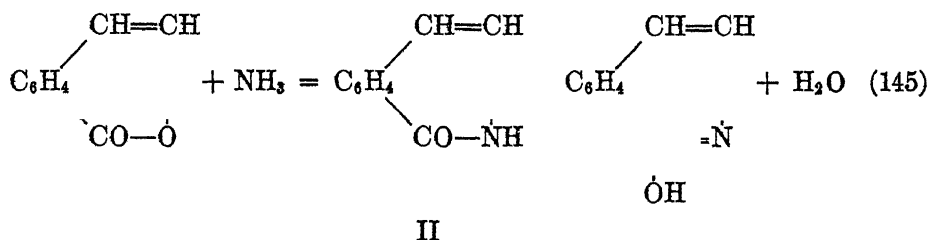
The isocoumarincarboxylic acids are readily converted into the corresponding isocarbostyrylcarboxylic acids, generally by short contact with ammonia at ordinary temperatures (29, 30, 32, 244). It will be noted that isocoumarin (I), a cyclic aquo ester, is ammonolyzed to isocarbostyryl (II), a cyclic ammono aquo acid ester.

The isocarbostyryls may be distilled with zinc dust and so converted to isoquinolines, or they may be heated, generally under pressure, with phosphorus oxychloride to give chloroisoquinolines. These latter are then reduced to the corresponding isoquinoline by heating with hydrogen iodide and red phosphorus. A typical preparation of 3-phenylisoquinoline is shown in the equation that follows (361):

$$\underset{C_6H_4}{\overset{CH=CC_6H_5}{\diagdown}} \quad \overset{POCl_3}{\longrightarrow} \underset{C_6H_4}{\overset{CH=CC_6H_5}{\diagdown}} \quad \overset{HI, P}{\underset{170°C.}{\longrightarrow}} \underset{C_6H_4}{\overset{CH=CC_6H_5}{\diagdown}}$$

$$\underset{\overset{|}{O}H}{C}==\overset{\cdot}{N} \qquad \qquad =\overset{\cdot}{N} \qquad \qquad CH=\overset{\cdot}{N}$$
$$\overset{\cdot}{C}l \qquad \qquad (146)$$
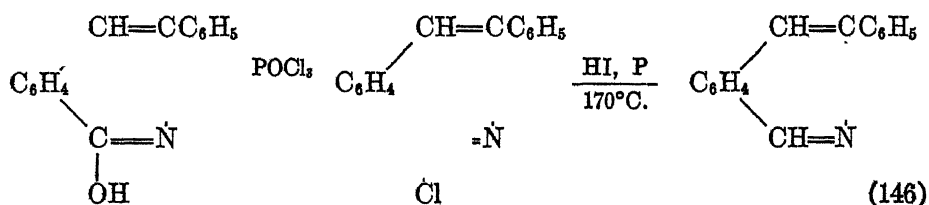
1,4-Dichloro-3-phenylisoquinoline is reduced by refluxing with hydrogen iodide solution and red phosphorus to 4-chloro-3-phenylisoquinoline, showing the greater mobility of the chlorine in the 1-position (361).

Dieckmann and Meiser (244) report the preparation of isocarbostyryl-4-carboxylic acid and its esters by the following series of reactions.

$$\underset{C_6H_4}{\overset{COOC_2H_5}{\diagdown}} \quad \overset{HCOOC_2H_5}{\underset{Na}{\longrightarrow}} \underset{C_6H_4}{\overset{COOC_2H_5}{\diagdown}} \quad \overset{\text{heat 2 hr. on}}{\underset{\underset{-C_2H_5ONa}{\text{water bath}}}{\longrightarrow}}$$

$$\underset{CH_2COOC_2H_5}{} \qquad \qquad CCOOC_2H_5$$
$$\overset{\|}{CHONa}$$

Ethyl homophthalate

$$
\underset{\substack{\text{C}_6\text{H}_4}}{\overset{\displaystyle\text{CO—O}}{\diagup}}\quad
\underset{\overset{\displaystyle|}{\text{COOC}_2\text{H}_5}}{\overset{\displaystyle`\text{C}=\text{CH}}{|}}
\xrightarrow[\text{room temp.}]{\text{NH}_3}
\underset{\substack{\text{C}_6\text{H}_4}}{\overset{\displaystyle\text{CO—NH}}{\diagup}}\quad
\underset{\overset{\displaystyle|}{\text{COOC}_2\text{H}_5}}{\overset{\displaystyle`\text{C}=\text{CH}}{|}}
\xrightarrow[\text{warm}]{\text{conc. HCl}}
$$

Ethyl isocarbostyryl-
4-carboxylate

$$
\underset{\substack{\text{C}_6\text{H}_4}}{\overset{\displaystyle\text{CO—O}}{\diagup}}\quad
\underset{\overset{\displaystyle|}{\text{COOH}}}{\overset{\displaystyle\text{C}=\text{CH}}{|}}
\xrightarrow[\text{room temp.}]{\text{NH}_3}
\underset{\substack{\text{C}_6\text{H}_4}}{\overset{\displaystyle\text{CO—NH}}{\diagup}}\quad
\underset{\overset{\displaystyle|}{\text{COOH}}}{\overset{\displaystyle\text{C}=\text{CH}}{\diagdown}}
\qquad(147)
$$

Isocarbostyryl-4-
carboxylic acid
(as ammonium salt)
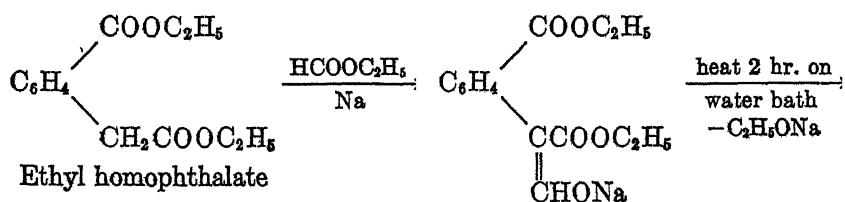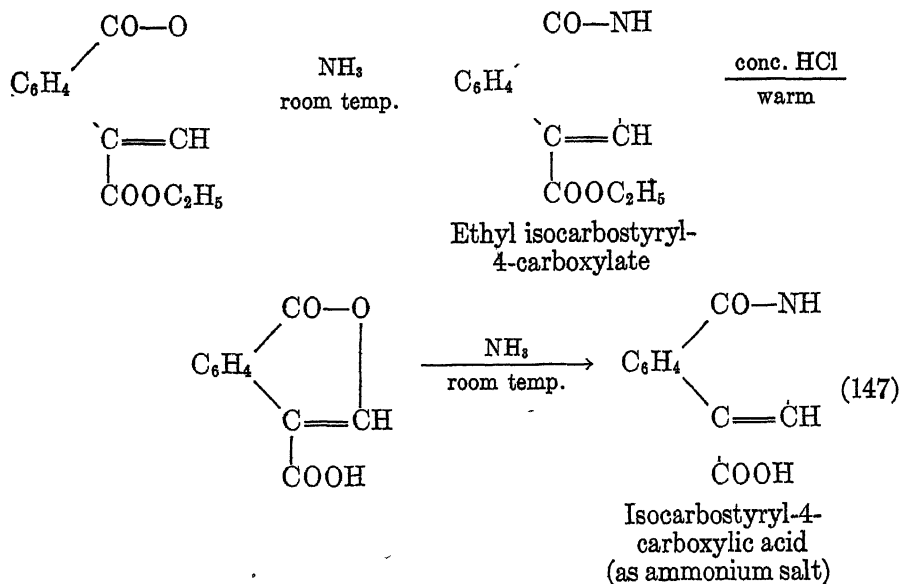
Homophthalimide (III) is tautomeric with 1,3-dihydroxyisoquinoline (IV) and is made (364, 365, 685) from homophthalic acid (696), which can be prepared from the commercially available phthalide.

$$
\underset{\substack{\text{C}_6\text{H}_4}}{\overset{\displaystyle\text{CH}_2\text{CO}}{\diagup}}\quad\overset{\displaystyle}{`\text{CO—NH}}
\qquad\qquad
\underset{\substack{\text{C}_6\text{H}_4}}{\overset{\displaystyle\text{CH}=\text{COH}}{\diagup}}\quad
\underset{\overset{\displaystyle|}{\text{OH}}}{\overset{\displaystyle\text{C}=\text{N}}{\diagdown}}
$$

III   IV
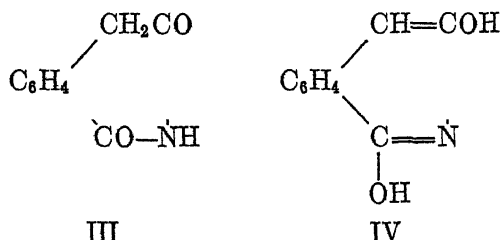
Other methods for preparing isocarbostyryl will be discussed later (see Section V, D).

5. Tetrahydroisoquinoline syntheses

1,2,3,4-Tetrahydroisoquinolines may be formed by reducing the 3,4-dihydro-isoquinolines, or the isoquinolines themselves, with tin and concentrated hydrochloric acid on a water bath (292a, 358, 431) or with sodium and absolute alcohol (31, 564a). The N-alkyl-1,2,3,4-tetrahydroisoquinolines are prepared by reducing the isoquinoline iodoalkylates (or halogenoalkylates), generally with tin and concentrated or fuming hydrochloric acid (105a, 807d). Isoquinoline may also be hydrogenated to 1,2,3,4-tetrahydroisoquinoline in the presence of platinum oxide (702a).

Of greater interest in connection with this review is the synthesis of tetra-hydroisoquinolines by the action of formaldehyde or methylal on substituted β-

phenethylamines in strong hydrochloric acid (105, 195a, 206, 208, 520b, 689, 690, 703),   The reactions follow the equations below:

$$C_6H_5{\diagup}^{CH_2CH_2}_{NH_2} + HCHO = C_6H_5{\diagup}^{CH_2CH_2}_{N} + H_2O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad CH_2$$

$$\qquad I \qquad\qquad\qquad\qquad\qquad\qquad II$$

$$II \xrightarrow{HCl} C_6H_4{\diagup}^{CH_2CH_2}_{CH_2NH} \cdot HCl \qquad\qquad (148)$$

$$\qquad\qquad\qquad\qquad\qquad III$$
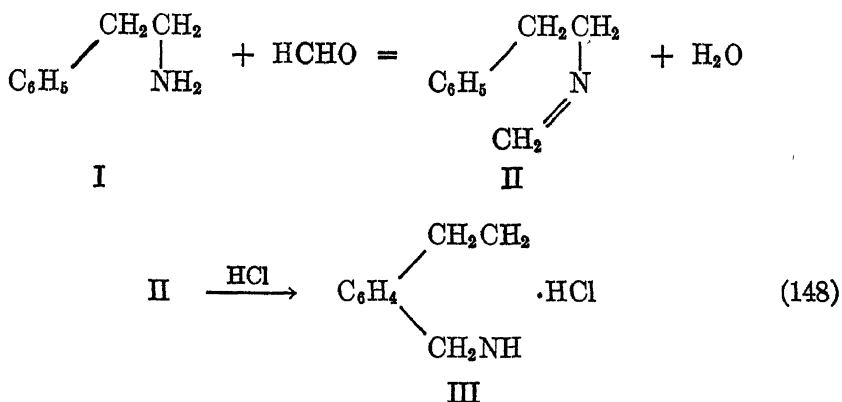
The Schiff base, such as the formal-β-phenethylamine (II) in the equation above, may often be isolated and then cyclized with hydrochloric acid, sulfuric acid, hydrobromic acid, or phosphorus oxychloride as catalysts.   It is possible that the agent active in the condensation is the carbinol amine, or ammono aquo mero-acetal, of the formula (IV) below:

$$C_6H_5{\diagup}^{CH_2CH_2-NH}_{HOCH_2} \qquad \overset{+}{\underset{CH_2}{-NH}}$$

$$\qquad IV \qquad\qquad\qquad V$$
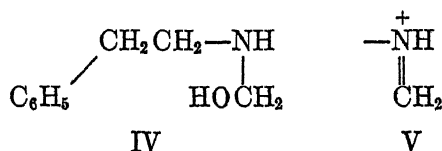
the product of addition of β-phenethylamine to formaldehyde.   Ring closure in any event has been effected by attack of the aldehydic terminal of a side chain upon an ortho position of the ring, according to the conditions laid down by Staub (775).   The aldehydic cation, V, of a salt of II is a more likely intermediate.

It is reported by Cooke and Gulland (181) that good yields of isoquinolines are formed by catalytic dehydrogenation of the corresponding tetrahydroisoquinoline with palladous chloride, though they remark that the method probably will not find general use.

B. ISOQUINOLINE RING OPENINGS

Very few openings of the isoquinoline ring appear to have been described; some are listed below.

(1) Papaverine halogen alkylates (I), when treated with alkalies, give a nitrogen-free phenolic compound (VII), probably in accordance with the equations below (185, 209, 214):
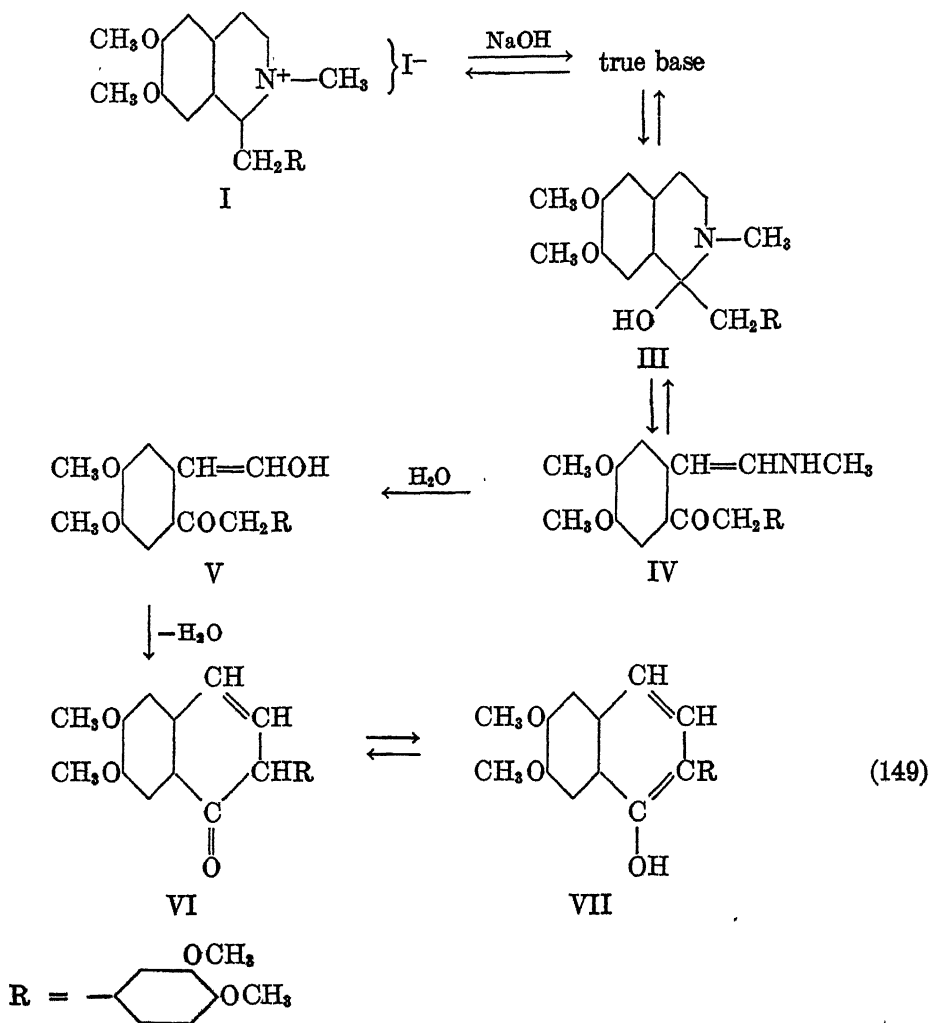
Here it is assumed that the pseudo base (III) is in equilibrium with the open-chain aldehyde form (IV) which is to be considered an ammono enol ether insofar as the grouping —CH=CHNHCH₃ is concerned. All substances of this class are readily hydrolyzed to the water system equivalent, —CH=CHOH or —CH₂CHO. Ring closure, V → VI, is the result of a Claisen reaction. 1-Benzyl-isoquinoline methiodide is similarly converted to 2-phenyl-1-naphthol (186).·

(2) Attempts to open the isoquinoline ring by the action of benzoyl chloride and alkali failed (708; see Section IV, F). Quaternary salts are formed when isoquinoline is heated with 2,4-dinitrochlorobenzene or with 1-chloro-2,4-dinitronaphthalene, but neither could be changed to glutacondialdehyde derivatives, as in the case of the corresponding pyridines. The reaction instead follows the rather unusual course below:

$$\underset{\underset{\text{VIII}}{}}{C_6H_4}\diagup^{CH=CH}_{\diagdown CH=\overset{+}{N}C_6H_3(NO_2)_2} \quad Cl^- + C_6H_5NH_2 \longrightarrow$$

$$\underset{\underset{\text{X}}{}}{C_6H_4}\diagup^{CH=CH}_{\diagdown CH=\overset{+}{N}C_6H_5} \quad Cl^- + C_6H_3(NO_2)_2NH_2 \quad (150)$$

$$\text{IX}$$
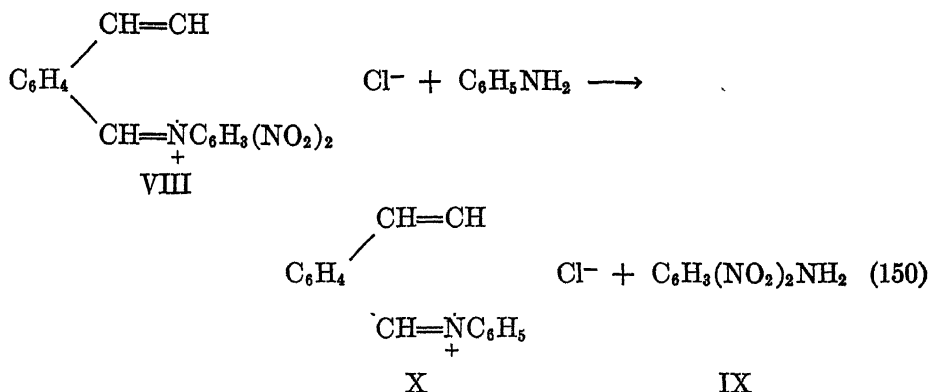
Zincke and Weisspfenning (839b) believe that the dinitrophenyl group is directly replaced by phenyl without ring opening, though this latter alternative seems much more probable. Aniline could react with the quaternary salt (VIII) to give an intermediate (XI), from which phenylisoquinolinium chloride (X) might be formed by a subsequent ring closure with loss of dinitroaniline.

$$\underset{\underset{\text{XI}}{}}{C_6H_4}\diagup^{CH=CHNHC_6H_5}_{\diagdown CH=\overset{+}{N}HC_6H_3(NO_2)_2}$$
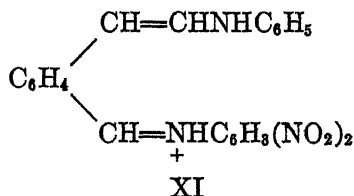
The single bond between the nitrogen and the 3-carbon atom of the dinitrophenylisoquinolinium chloride has been opened by adding the elements of aniline to the molecule. It is perhaps more reasonable to assume that aniline adds to the aldehydic $-CH=\overset{+}{N}-$ group to give XII, the tautomeric form of which can lose dinitroaniline to form phenylisoquinolinium chloride (X).

$$\underset{\underset{\text{XII}}{}}{C_6H_4}\diagup^{CH=CH}_{\diagdown \underset{\underset{\underset{C_6H_5}{|}}{\overset{|}{NH}}}{CH-\overset{+}{N}HC_6H_3(NO_2)_2}} \quad \rightleftarrows \quad \underset{\underset{\text{XIII}}{}}{C_6H_4}\diagup^{CH=CH-NHC_6H_3(NO_2)_2}_{\diagdown \underset{\underset{\overset{+}{N}HC_6H_5}{\|}}{CH}}$$
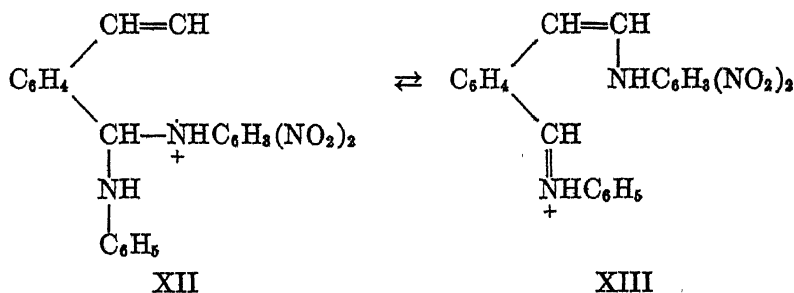
2,4-Dinitrophenylisoquinolinium chloride (VIII) reacts with warm alcoholic phenylhydrazine to give a well-crystallized black phenylhydrazone, apparently through an intermediate reddish brown solid (XIV) that may be isolated by working at lower temperatures. Zincke and Weisspfenning (839) interpret the reaction in the following manner:

$$\underset{\underset{+}{\overset{\displaystyle CH=CH}{C_6H_4}}{\overset{\diagup}{\diagdown}}}{CH=NC_6H_3(NO_2)_2} \quad Cl^- \quad \xrightarrow[C_2H_5OH \,+\, H_2O]{C_6H_5NHNH_2}$$

VIII ⁻

$$C_6H_4 \overset{\diagup}{\underset{\diagdown}{}} \begin{array}{l} CH=CH \\ CH-NC_6H_3(NO_2)_2 \\ \underset{OH}{|} \end{array}$$

XIV

$$XIV \;+\; C_6H_5NHNH_2 \;\rightarrow\; C_6H_4\overset{\diagup}{\underset{\diagdown}{}}\begin{array}{l} CH=CHNHC_6H_3(NO_2)_2 \\ \\ CH(OH)NHNHC_6H_5 \end{array} \qquad \xrightarrow{-H_2O}$$

XV

$$C_6H_4\overset{\diagup}{\underset{\diagdown}{}}\begin{array}{l} CH=CHNHC_6H_3(NO_2)_2 \\ \\ CH=NNHC_6H_5 \end{array} \qquad \qquad (150a)$$

XVI
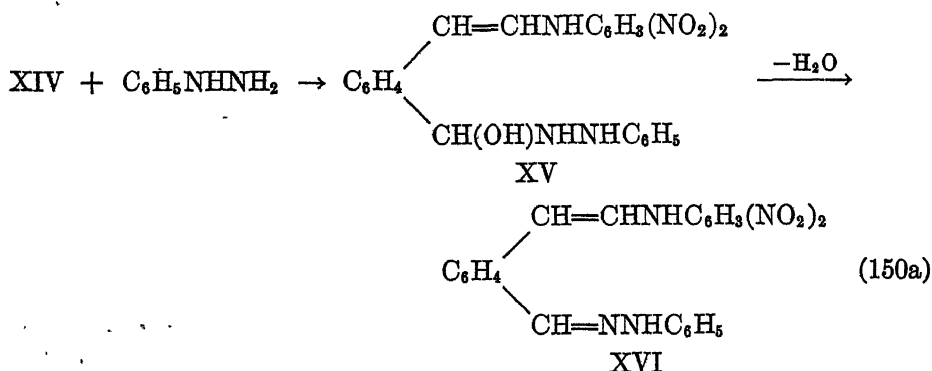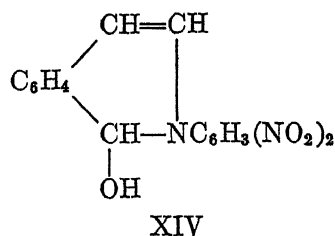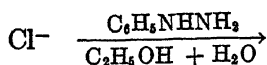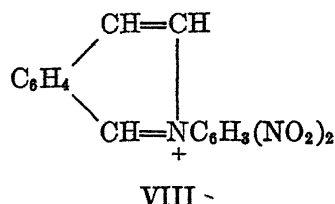
The phenylhydrazone (XVI) is believed to have the open-chain formula shown, though the evidence does not seem to be too conclusive. The reddish pseudo base (XIV) is also formed by the action of alkali, or of water solutions of aniline and aliphatic amines on dinitrophenylisoquinolinium chloride (VIII).

Similar reactions have been recorded for 2,4-dinitronaphthylisoquinolinium chloride (837).

(3) Cotarnine and hydrastinine, pseudo bases of the isoquinoline series (see Section V, I–J), have sometimes been given the structures of open-chain methyl-amino aldehydes because of their high aldehydic reactivity, even though the majority of observers seem to prefer the cyclic formula. Nevertheless, it appears that several of the compounds formed chemically from cotarnine and hydrastinine have open-chain configurations.

(4) Oxidation of isoquinoline and its substitution products often leads to the partial disruption of the pyridine nucleus, but these reactions are of little interest here, though they are, in a sense, ring openings. As an example, about equal parts of phthalic acid and pyridine-3,4-dicarboxylic acid (cinchomeronic acid) are formed when isoquinoline is oxidized with alkaline permanganate (430; cf. 376).

(5) When 2,4-dinitrophenyl-6,7-dimethoxyisoquinolinium chloride is re-

fluxed for 5–6 hr. with 2 moles of aniline, there results a quantitative yield of 2,4-dinitrodiphenylamine with the simultaneous formation of 6,7-dimethoxyisoquinoline (447). Here dinitrochlorobenzene, formed by slight dissociation of the quaternary salt, was continually removed by the aniline, with which it reacted to give the dinitrodiphenylamine. Under similar conditions, the pyridine ring would have been opened.

<div style="text-align:center">

C. REACTION OF ISOQUINOLINE WITH METALS AND WITH
METALLOÖRGANIC COMPOUNDS

</div>

Isoquinoline adds two atoms of sodium in liquid ammonia at −33°C. (60) in either the 1,2- or the 1,4-positions. If the nitrogen atom has sodium attached to it, the addition can only have been in the 1,2-position. When isoquinoline and potassium are heated together at about 100°C., and then finally at 170–180°C. and allowed to cool in air, isocarbostyril is formed in yields that do not exceed about 10 per cent of the theoretical (291). The action of sodium on isoquinoline gave only a very small amount of diisoquinolyl (291a).

The synthesis of isocarbostyril in the above reaction can be explained by saying that potassium adds to isoquinoline to give a 1,2-addition product, which is oxidized by air to the potassium salt of 1-hydroxyisoquinoline and, presumably, also to some oxide of potassium. The over-all process amounts to the oxidation of a cylic ammono aldehyde ether, isoquinoline, to a cylic ammono aquo acid ester, isocarbostyril.

Ethylmagnesium bromide reacts with isoquinoline in diethyl ether at 140–160°C. to form 1-ethylisoquinoline (62), while phenylmagnesium bromide and benzylmagnesium chloride (the latter in dioxane) give 1-phenylisoquinoline and 1-benzylisoquinoline, respectively (46).

Isoquinoline reacts somewhat more readily with the lithium alkyls than with the Grignard reagent (828). Thus, hydrolysis of the product of the reaction of butyllithium with isoquinoline in benzene gives 1-butyl-1,2-dihydroisoquinoline, which is easily oxidized to 1-butylisoquinoline by heating with nitrobenzene.

<div style="text-align:center">

D. 1-HYDROXYISOQUINOLINE AND 1-AMINOISOQUINOLINE

</div>

Chichibabin (143a) prepared 1-hydroxyisoquinoline (isocarbostyril) by heating isoquinoline with dry potassium hydroxide at 220°C. for about 3.5 hr. This type of reaction, an oxidation of a cyclic ammono aldehyde ether to a cyclic ammono aquo acid ester, has been discussed in Sections II, G and IV, G (cf. 808).

There is at least one statement on record to the effect that hydroxyl in position 1 is more readily replaced by chlorine than in position 4. Gabriel and Colman (366) heated 1,4-dihydroxyisoquinoline with phosphorus oxychloride at 160–170°C. and obtained 1-chloro-4-hydroxyisoquinoline, together with a small amount of 1,4-dichloroisoquinoline. However, it is reported (368) that 1,4-dihydroxy-3-methylisoquinoline is reduced by hydrogen iodide and red phosphorus at 180°C. to 3-methylisocarbostyril, indicating the higher mobility of the 4-hydroxyl group.

1-Aminoisoquinoline may be prepared by heating isoquinoline with sodium

amide under neutral solvents, though the yields are not very good (149). There is some improvement (to about 65 per cent of the theoretical) if the fused eutectic of sodium amide and potassium amide (541) is used in place of sodium amide (793). In liquid ammonia, isoquinoline reacts with an excess of potassium amide to form aminoisoquinoline in yields of 70 per cent or over, together with an equivalent quantity of hydrogen gas (49, 56).

$$C_6H_4\begin{matrix}CH{=}CH\\ \\CH{=}N\end{matrix} + KNH_2 = C_6H_4\begin{matrix}CH{=}CH\\ \\C{=}N\\ \\NHK\end{matrix} + H_2$$

$$C_6H_4\begin{matrix}CH{=}CH\\ \\C{=}N\\ \\NHK\end{matrix} + H_2O = C_6H_4\begin{matrix}CH{=}CH\\ \\C{=}N\\ \\NH_2\end{matrix} + KOH \quad (151)$$
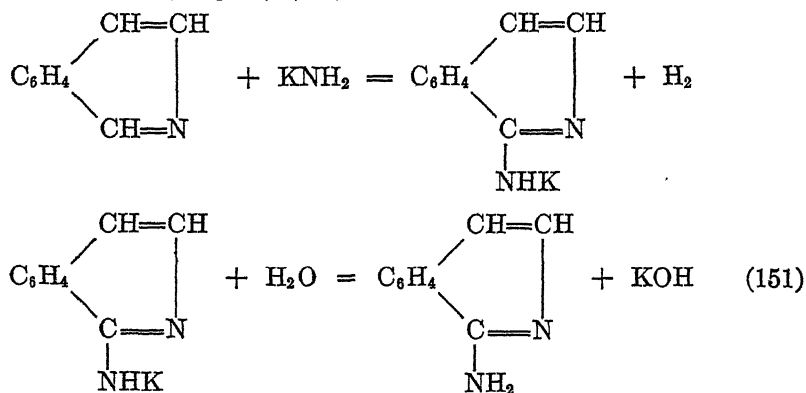
Isoquinoline has therefore been nitridized to a cylic ammono acid ester.

E. 1-CHLOROISOQUINOLINE, 4-BROMOISOQUINOLINE, 1-ALKOXY-ISOQUINOLINES, N-ALKYLISOQUINOLONES

1-Chloroisoquinoline is made by the action of the oxychloride and pentachloride of phosphorus on N-methylisoquinolone (314, 315) (cf. Section IV, H), or of the former on isocarbostyryl (367a). 4-Bromoisoquinoline may be prepared by heating the hydrobromide perbromide of isoquinoline for about 7 hr. at 180–190°C. (65c, 181a, 267b).

Isoquinolines with a chlorine in the 1-position are reduced by hydrogen iodide (b.p. 127°C.) and red phosphorus at 170–180°C. to the corresponding isoquinoline, in accordance with the equation (361, 367, 370):

$$C_6H_4\begin{matrix}CH{=}CCH_3\\ \\C{=}N\\ \\Cl\end{matrix} + 2HI = HCl + 2I + C_6H_4\begin{matrix}CH{=}CCH_3\\ \\CH{=}N\end{matrix} \quad (152)$$
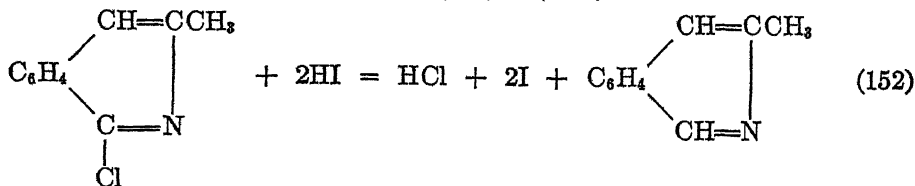
A comparison of the reactivity of chlorine in the 1- and 3-positions was made by heating 1,3-dichloroisoquinoline with hydrogen iodide and red phosphorus at 150–170°C., or by warming with tin and hydrochloric acid in glacial acetic acid solution. 3-Chloroisoquinoline is formed in both cases, indicating the higher mobility of halogen in the 1-position, in accordance with expectations (cf. Section IV, H). (1-Chloroisoquinoline is a cyclic ammono acid chloride ester.) Similarly, 1,4-dichloro-3-phenylisoquinoline may be reduced to 3-phenyl-4-chloroisoquinoline (362a).

When 1-chloroisoquinolines are warmed with alcoholic solutions of potassium

hydroxide, or of the alkali-metal alkoxides, the halogen is replaced by an alkoxyl group, as in the following example (363):

$$\underset{\overset{|}{\underset{\displaystyle Cl}{C=N}}}{\overset{\displaystyle CH=CC_6H_5}{C_6H_4}} + NaOC_2H_5 = \underset{\overset{|}{\underset{\displaystyle OC_2H_5}{C=N}}}{\overset{\displaystyle CH=CC_6H_5}{C_6H_4}} + NaCl \quad (153)$$
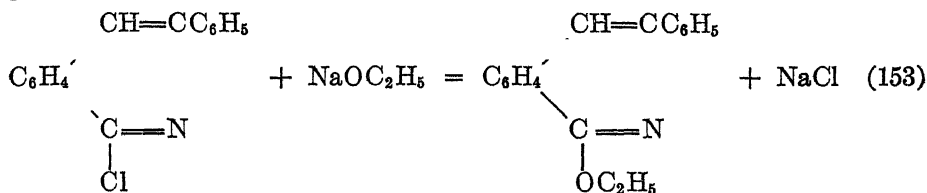
1,4-Dichloro-3-methylisoquinoline, when heated for 0.75 hr. with sodium methoxide in methanol at 100°C., similarly gives 4-chloro-1-methoxymethyliso-quinoline, showing that the 1-chlorine is most readily replaced (369). 1-Alkoxyl-3-propyl (or isopropyl)isoquinolines have been made in the same way (7,557), while 1-methoxyisoquinoline has also been prepared by heating the silver salt of isocarbostyril with methyl iodide at 100°C. (292). 1-Chloro-3-phenylisoquino-line and aniline react when heated to give anilinophenylisoquinoline (281c).

4-Bromoisoquinoline is converted to 4-cyanoisoquinoline (799) or to 4-amino-isoquinoline (181a) by heating with cuprous cyanide (0.75 hour at 250°C.) or with concentrated aqueous ammonia and copper sulfate (16 hr. at 165–170°C.), respectively. When heated with sodium methylate in methanol (7 hr. at 235°C.), 4-bromoisoquinoline is reduced to isoquinoline in about 50 per cent yield (65c).

2-Methyl-1-isoquinolone, a cyclic ammono aquo ester,

$$\underset{\overset{\displaystyle}{\underset{\displaystyle CO-NCH_3}{\diagdown}}}{\overset{\displaystyle CH=CH}{\underset{\diagup}{C_6H_4}}}$$
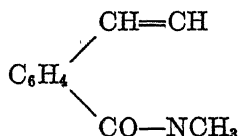
is formed by heating isocarbostyril for several hours with methyl alcoholic po-tassium hydroxide (292), by oxidizing methylisoquinolinium iodide with alkaline potassium ferricyanide (198, 314), or by the action of a primary amine (CH₃NH₂) on isocoumarin (32).

The carbonyl group in 2-methyl-1-isoquinolone should resemble that in an ester, though its reactivity appears to be somewhat less. Decker and Pschorr (230) have thus prepared 1-benzylidene-2-methyl-1,2-dihydroisoquinoline by the following reaction:

$$\underset{\overset{\displaystyle}{\underset{\displaystyle CO-NCH_3}{\diagdown}}}{\overset{\displaystyle CH=CH}{\underset{\diagup}{C_6H_4}}} + C_6H_5CH_2MgCl = \underset{\overset{|}{\underset{\displaystyle CH_2C_6H_5}{\diagdown}}}{\overset{\displaystyle OMgCl}{\underset{\diagup}{-C-NCH_3-}}} \quad H_2O$$

$$\underset{\overset{|}{\underset{\displaystyle CH_2C_6H_5}{\diagdown}}}{\overset{\displaystyle OH}{\underset{\diagup}{-C-NCH_3-}}} \quad \overset{-H_2O}{\longrightarrow} \quad \underset{\overset{\displaystyle C-NCH_3}{\underset{\displaystyle \overset{||}{CHC_6H_5}}{\diagdown}}}{\overset{\displaystyle CH=CH}{\underset{\diagup}{C_6H_4}}} \quad (154)$$
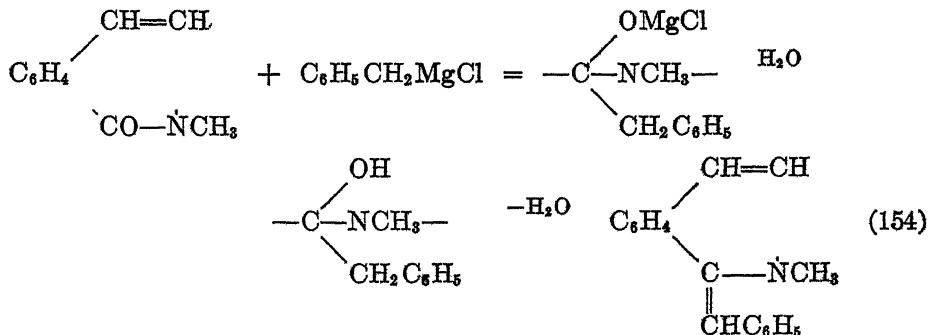
None of the intermediates was isolated (see also 229a).

A mixture of phosphorus pentachloride and phosphorus oxychloride reacts with 2-methyl-1-isoquinolone to form 1-chloroisoquinoline (314–315).

F. 1-ALKYLISOQUINOLINES

Mills and Smith (625; *cf.* 760b) showed many years ago that the methyl in 1-methylisoquinoline (I) had ketonic reactivity, while a methyl in the 3-position was inactive, presumably because of the impossibility of a tautomerism of the latter in the sense of the following equation:

$$C_6H_4 \underset{\overset{|}{\underset{CH_3}{\cup}}{=\dot{N}}}{\overset{CH=CH}{<}} \qquad\qquad C_6H_4 \underset{\overset{-\ddot{N}H}{\underset{\ddot{C}H_2}{}}}{\overset{CH=CH}{<}} \qquad (155)$$

$$\text{II}$$
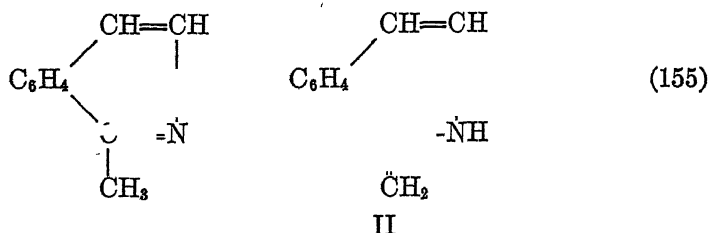
The characteristic behavior of the 1-alkylisoquinolines is considered to be due, at least in part, to the enamic or ammono enolic, form (II).

1-Styrylisoquinoline (III) may be prepared by heating 1-methylisoquinoline with an equimolar quantity of benzaldehyde and a small quantity of zinc chloride at 100°C. (623).

$$C_6H_4 \underset{\overset{|}{\underset{CH=CHC_6H_5}{C=N}}}{\overset{CH=CH}{<}}$$

$$\text{III}$$
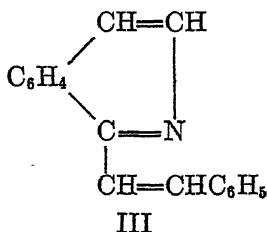
The preparation of the styryl derivatives of a number of substituted isoquinolines has been patented (665).

Papaverine (IV) reacts with alkali-metal amides in liquid ammonia to form red salts (60), and with aqueous formaldehyde at 100°C. (20 hr.) to give methylene papaverine ($=CH_2 \rightarrow =C=CH_2$) (492, 769; *cf.* 337). Furthermore, papaverine is readily oxidized by mercuric acetate in acetic acid solution to papaverinol ($=CH_2 \rightarrow =CHOH$) (371c) and with cold dilute acid permanganate to papaveraldine ($=CH_2 \rightarrow =C=O$) (375b), indicating again that the methylene group is reactive.

$$\text{IV}$$
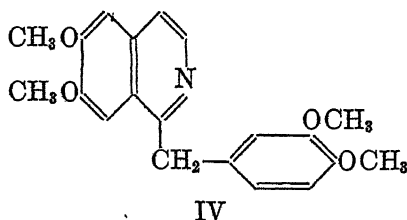
G. ISOQUINOLINE ALKYL HALIDES

1. Pseudo bases and methylene bases

Quaternary isoquinolinium salts (I) react with alkali to form a strongly basic solution which contains a small amount of the pseudo base (III), together with a larger quantity of the true base (II). Benzene extracts the pseudo base from this mixture, and water will in turn extract the true base from the benzene, indicating clearly the influence of solvent upon the point of equilibrium (222a; see also 163, 164, 166, 193a, 224a, 792).

Oxidation of a mixture of a quaternary quinolinium salt and alkali by means of potassium ferricyanide gives 2-methyl-1-isoquinolone (IV), an ammono aquo ester, in accordance with the equation (198a, 314):

$$
\begin{array}{ccc}
& \text{CH=CH} & \\
\text{C}_6\text{H}_4 \big\langle \quad \big| & \text{I}^- \quad + \text{NaOH} \rightleftarrows \\
& \text{CH=N}^+ \; \text{C}_7\text{H}_7\text{SO}_3^- \\
& \quad\; | \qquad \text{etc.} \\
& \text{CH}_3 \\
& \quad\text{I}
\end{array}
$$

$$
\text{II} \quad \text{OH}^- \rightleftarrows \quad \text{III} \quad \xrightarrow[\text{NaOH}]{\text{K}_3\text{Fe(CN)}_6} \quad \text{IV} \quad (156)
$$

where

II: $\text{C}_6\text{H}_4 \big\langle \begin{smallmatrix} \text{CH=CH} \\ | \\ \text{CH=N}^+ \\ | \\ \text{CH}_3 \end{smallmatrix}$

III: $\text{C}_6\text{H}_4 \big\langle \begin{smallmatrix} \text{CH=CH} \\ | \\ \text{CH—NCH}_3 \\ | \\ \text{OH} \end{smallmatrix}$

IV: $\text{C}_6\text{H}_4 \big\langle \begin{smallmatrix} \text{CH=CH} \\ | \\ \text{CO—NCH}_3 \end{smallmatrix}$

2,4-Dinitrophenylisoquinolinium chloride (V)

V: $\text{C}_6\text{H}_4 \big\langle \begin{smallmatrix} \text{CH=CH} \\ | \\ \text{CH=NC}_6\text{H}_3(\text{NO}_2)_2 \\ + \end{smallmatrix}$ } Cl⁻

VI: $\text{C}_6\text{H}_4 \big\langle \begin{smallmatrix} \text{CH=CH} \\ | \\ \text{CH—NC}_6\text{H}_3(\text{NO}_2)_2 \\ | \\ \text{OH} \end{smallmatrix}$
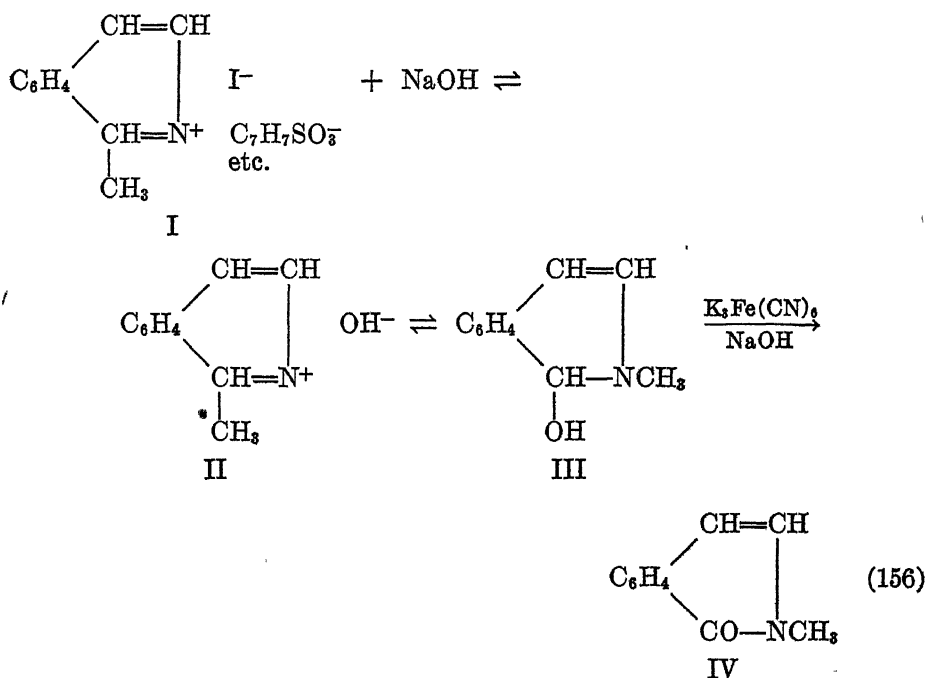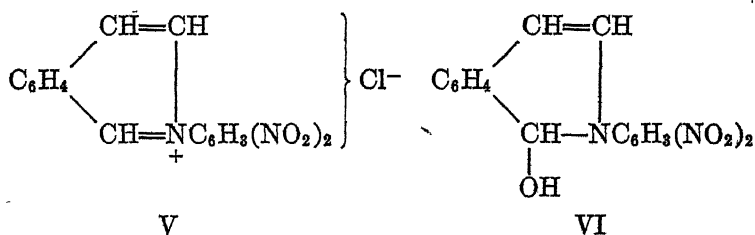
may be prepared by heating 2,4-dinitrochlorobenzene with isoquinoline. When treated with alkalies, soda, ammonia or primary amines in aqueous solution, a red pseudo base (VI) is formed, and this may readily be converted to red crystal-

line oxygen ethers (OH of formula VI → OR) by boiling with methyl alcohol or ethyl alcohol. The pseudo base, a cyclic ammono aquo meroacetal, has been changed to a cyclic ammono aquo acetal. The alkoxy groups can be interchanged by boiling the oxygen ether with another alcohol, showing their high mobility (839a). Similar results have been recorded for dinitronaphthylisoquinolinium chloride (837).

By the action of alkalies on quaternary salts of papaverine (VII) Claus and his students (for references see 224a) obtained compounds which were subsequently called "isopapaverines" by Decker and Klauser (224a). A typical preparation is the following (224a; cf. 224, 231, 226):

VII   VIII
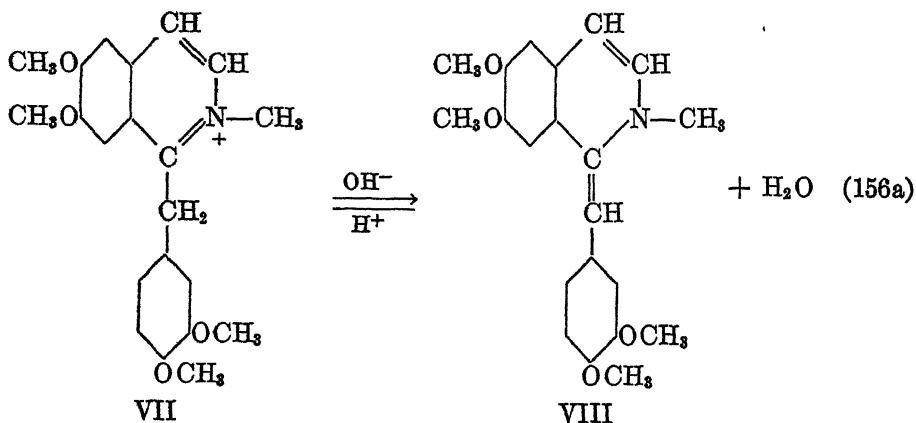
The cation (VII) of methylpapaverinium iodide is attacked by hydroxyl ion to give VIII, a "methylene base", either through the intermediate pseudo base,

$$RC-N-CH_3$$
$$OH$$
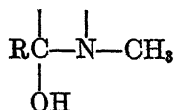
or by removal of an ionizable hydrogen from the methylene group between the two nuclei. The isopapaverine (VIII), when shaken with water or when treated with acids, reverts to the strong base, N-methylpapaverinium hydroxide, or to its salts, respectively (cation = VII). The methylene base (VIII) precipitates when an aqueous solution of the quaternary ammonium base is concentrated.

The iodomethylate of 1-benzylisoquinoline (IX) reacts with sodium hydroxide to give the methylene base, 2-methyl-1-benzylidene-1,2-dihydroisoquinoline (X), as shown by the following equation:

IX   X
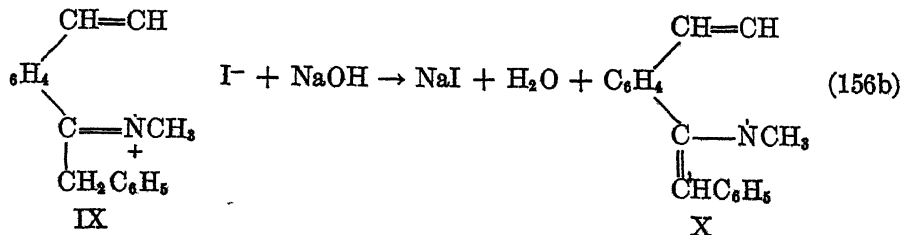
The same product is obtained by the action of benzylmagnesium chloride on 2-methyl-1-isoquinolone (230; equation 154). It is converted by hydrogen iodide to 1-benzylisoquinoline iodomethylate.

2. 1-p-Dimethylaminostyrylisoquinoline methiodide

This compound is made by boiling 1-methylisoquinoline methiodide with p-dimethylaminobenzaldehyde for 3 hr. in absolute alcohol solution with the addition of a little piperidine as a catalyst (622). 1-Methylisoquinoline reacts less readily with aldehydes.

3. 1-Iodoisoquinoline methiodide

This compound (XI) is prepared by heating 1-chloroisoquinoline methiodide with methyl iodide in a sealed tube for 2 days at 100°C. (315). The reaction is expressed by the equation:

$$
\begin{array}{ccc}
\underset{\displaystyle C_6H_4}{\overset{\displaystyle CH{=}CH}{\diagdown}} & & \underset{\displaystyle C_6H_4}{\overset{\displaystyle CH{=}CH}{\diagdown}} \\
\end{array}
$$

$$
\begin{matrix}
CH{=}CH & & & & CH{=}CH & & \\
\diagup & & & & \diagup & & \\
C_6H_4 & & I^- + CH_3I = & C_6H_4 & & I^- + CH_3Cl & (157) \\
\diagdown & & & & \diagdown & & \\
C{=}NCH_3 & & & & C{=}\overset{+}{N}CH_3 & & \\
| & & & & | & & \\
Cl & & & & I & & \\
& & & & XI & &
\end{matrix}
$$
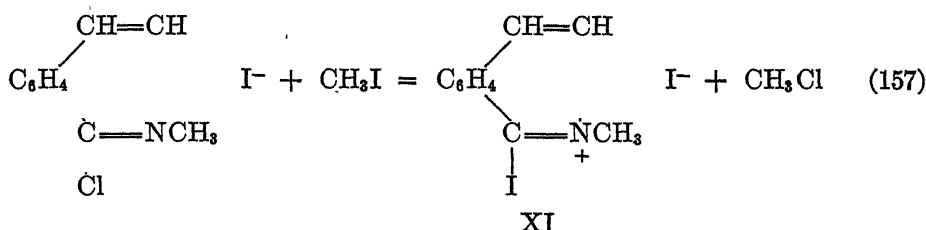
The activity of the iodine is so great that XI cannot be crystallized from water or alcohol without large losses, owing to the replacement of the iodine in the 1-position by hydroxyl or ethoxyl, respectively (313).

1-Aminoisoquinoline alkiodides are made readily by refluxing the 1-iodoisoquinoline alkiodides for about 10 min. with ammonia (315).

4. Isoquinoline alkiodides and the Grignard reagent

Isoquinoline alkiodides react with the Grignard reagent to form 1,2-dialkyl-1,2-dihydroisoquinolines in a manner similar to that of equation 112 (45, 335).

5. Isoquinoline, benzoyl chloride, and potassium cyanide

When these three substances are heated together, 1-cyano-2-benzoyl-1,2-dihydroisoquinoline is obtained (cf. Section IV, F and equation 69) (708). When hydrolyzed with 36 per cent hydrochloric acid for about a day at room temperature, there is formed a mixture of isoquinoline-1-carboxamide and isoquinoline-1-carboxylic acid, together with benzaldehyde. It was found somewhat better to heat the 2-benzoyl-1-cyano-1,2-dihydroisoquinoline with phosphorus pentachloride at 125–130°C. to obtain 1-cyanoisoquinoline, which acid hydrolysis converts to isoquinoline-1-carboxylic acid (375a, 453, 456).

6. Cyanine dyes containing the isoquinoline nucleus

The formation of cyanine dyes is dependent in large measure upon the aldehydic or ketonic reactivity of quaternary salts containing pyridine, quinoline, isoquinoline, benzothiazole, or related nuclei (see Section IV, N, 9). Fisher and

Hamer (313) have described the preparation of 2,1'- and 4,1'-cyanines derived from isoquinoline by condensing 1-iodoquinoline alkiodides with quinaldine alkiodides or lepidine alkiodides under alkaline conditions (see Section IV, N, 9, b, (1) and equation 134). The 2,1'-cyanines may also be made, though in much poorer yield, by heating the alkiodides of quinaldine and of isoquinoline in the presence of a base (*cf.* equations 130, 133). Isoquinoline red, a somewhat more complex cyanine, is obtained when isoquinoline and quinaldine are heated with benzotrichloride at 150°C. (802; *cf.* 739, 740).

H. DIHYDROISOQUINOLINES

The comparatively low aldehydic and ketonic reactivity of isoquinoline and its 1-alkyl and 1-aryl derivatives, respectively, has been explained as due to the effect of the resonance of the six-membered ring with three double bonds. The 3,4-dihydroisoquinolines are intermediates in the Bischler–Napieralski synthesis (Section V, A, 1), but the literature concerning their chemical properties is too scanty to permit of comparisons with the corresponding isoquinolines. It is expected that the former will behave more like open-chain compounds which

contain the groupings —CH=N— or RC=M—.

Pseudo bases and methylene bases are derivatives of 1,2-dihydroisoquinoline, but they have been described a few pages before. Hamilton and Robinson (413) heated 1-benzyl-3,4-dihydroisoquinoline with methyl sulfate in benzene and prepared a methosulfate, whose aqueous solution reacted with potassium hydroxide to give 1-benzylidene-2-methyl-1,2,3,4-tetrahydroisoquinoline. Apparently the chemistry of the dihydroisoquinolines and of the isoquinolines will be similar.

I. COTARNINE

Cotarnine (II or III) has probably been more intensively investigated than any other single pseudo base, both because of its high reactivity, and because of its availability as a product of the oxidation of narcotine (I) (9, 42, 818).

(158)
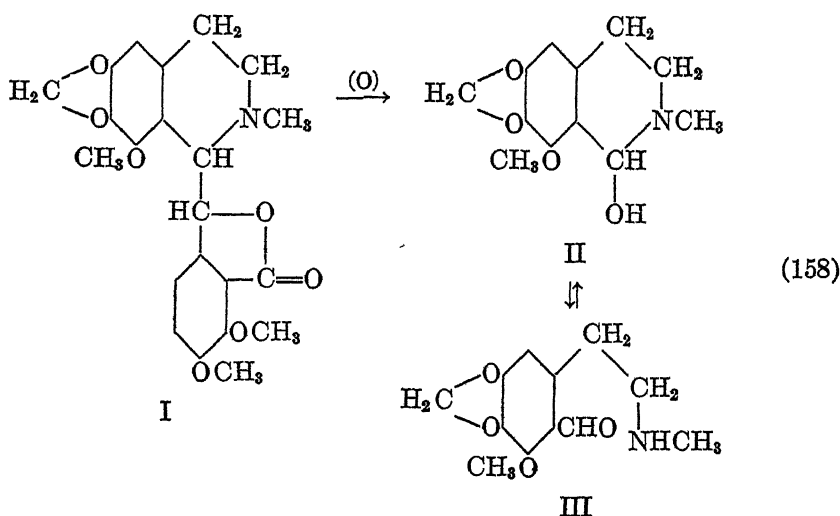
Narcotine (I) is an ammono ether, since the nitrogen has three indifferent groups attached to it; cotarnine, its oxidation product, is variously represented in the cyclic form of an ammono aquo meroacetal (II), (199; cf. 435) or as an open-chain aminoaldehyde (III) (237, 725; cf. 407). An analogous case of tautomerism of an open-chain aldehyde with a cyclic hemiacetal of the water system is encountered in glucose and other monosaccharides. Dobbie, Lander, and Tinkler (251) conclude as a result of an examination of the absorption spectra of cotarnine and its derivatives that the former in the solid state, in ether, or in chloroform has the structure shown in formula II above. The aqueous solution of cotarnine is yellow, and is believed to contain the strong ammonium base

$$(-CH=\overset{|}{\underset{+}{N}}-CH_3)OH^-$$
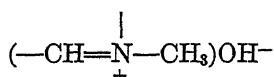
and no evidence was found for the existence of any forms other than the two that have been mentioned. A good discussion of the question of the constitution of this important alkaloidal derivative is given by Small and Lutz (767).

Decker and Becker (203) have synthesized cotarnine methosulfate by the following series of reactions:

(159)
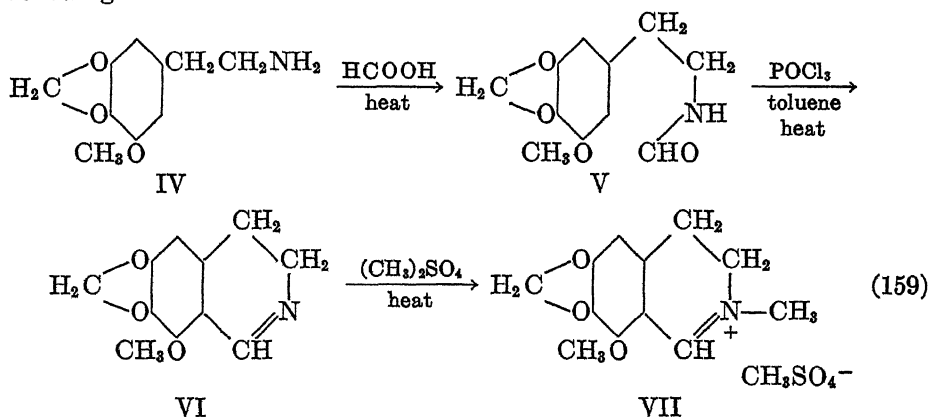
The quaternary salts of cotarnine (VII) are derivatives of 3,4-dihydroisoquinoline, while cotarnine itself is related to 1,2,3,4-tetrahydroisoquinoline. The iodide corresponding to VII is identical with cotarnine iodide.

The substances formed chemically by condensations involving cotarnine are generally given cyclic structures, though this is not always the case (cf. 237, 725). Hope and Robinson (434) have prepared anhydrocotarnine nitromethane (VIII) by the action of cotarnine on nitromethane at room temperatures, in accordance with the equation:

(160)
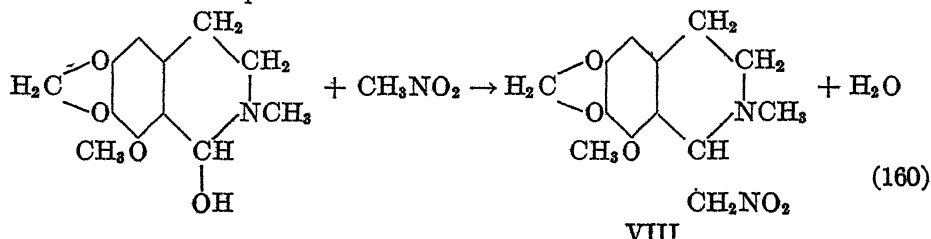
Anhydrocotarnine nitromethane forms two methiodides; the one produced in the smaller amount is probably the open-chain derivative, while the major product has the closed-chain structure. Along similar lines, it has been reported that glucose gives two phenylhydrazones (325), one of which is a cyclic, the other an open-chain, derivative.

A few of the condensations of cotarnine are listed below. It seems probable that the quaternary ammonium hydroxide form (formula VII above, $CH_3SO_4^-$ replaced by OH^-) is the true carrier of the reactions involved, rather than the pseudo, or carbinol, base (formula II above, equation 158; Robinson and Robinson (715a)).

(*1*) Cotarnine and absolute ethyl alcohol give in the cold an ethoxy derivative (IX) which is to be considered a cyclic ammono aquo acetal (333, 727, 728).

IX
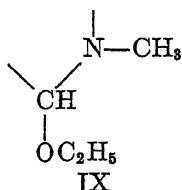
It is readily hydrolyzed by water into its components, and unexpectedly so, since acetals are as a class more stable. However, if it is converted to a methiodide, hydrolysis cannot be affected even by hot concentrated hydrochloric acid, apparently as a result of the additional stabilization given by the positively charged nitrogen (727; *cf*. 333).

Ethyl mercaptan, a thioalcohol, and cotarnine react (333a) to form a readily hydrolyzable thiol derivative containing the grouping,
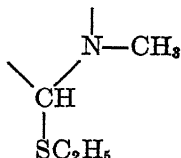
which is to be regarded as a cyclic thio ammono acetal.

(*2*) Cotarnine and its salts react with the Grignard reagent to give substituted hydrocotarnines of the general formula X (331):

X
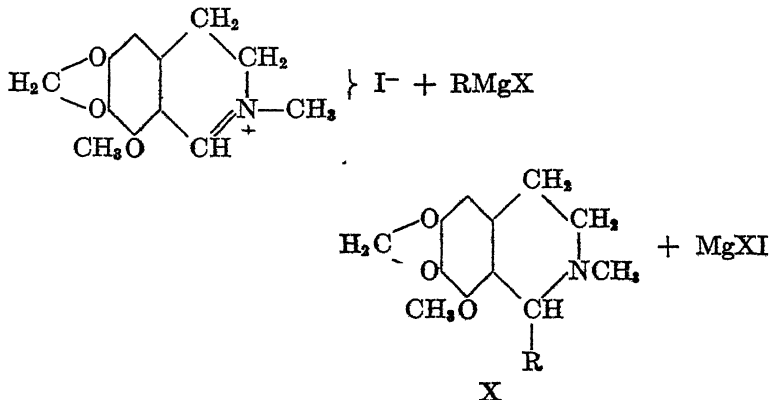
(*3*) Cotarnine condenses with a large number of compounds containing reactive hydrogen, or a reactive methyl or methylene group, to give products that have generally been considered cyclic, though some believe otherwise and think that the structure is dependent upon the nature of the reagent (238, 543, 562; *cf.* 240). The reactions are represented by the equation:

$$(161)$$

XI
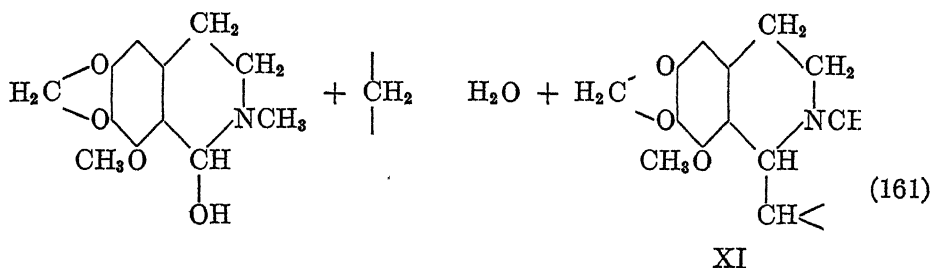
A partial list of substances that have been condensed with cotarnine is the following: The methyl ketones (240, 439, 559), resorcinol, pyrogallol, and other phenols (4, 564), acetoacetic esters (545, 561), amides and imides, including isatin (438, 440), nitrotoluenes and nitromethane (433), nitroveratrole and nitropiperonal (714a), nitroaldehydes of the aromatic series (3, 238, 450), *p*-aminoacetophenone and various aromatic amines (241, 334), hippuric acid, oxalacetic ester, phenylacetic acid, benzyl cyanide, and even fluorene and indene (438, 755), methyloxindole (694), phenyl isocyanate, phenyl isothiocyanate (239) and many others.

(*4*) Cotarnine reacts with phthalide, or better with 5-nitrophthalide (432), to yield narcotine-like compounds, as shown by the equation:

$$(162)$$

XII
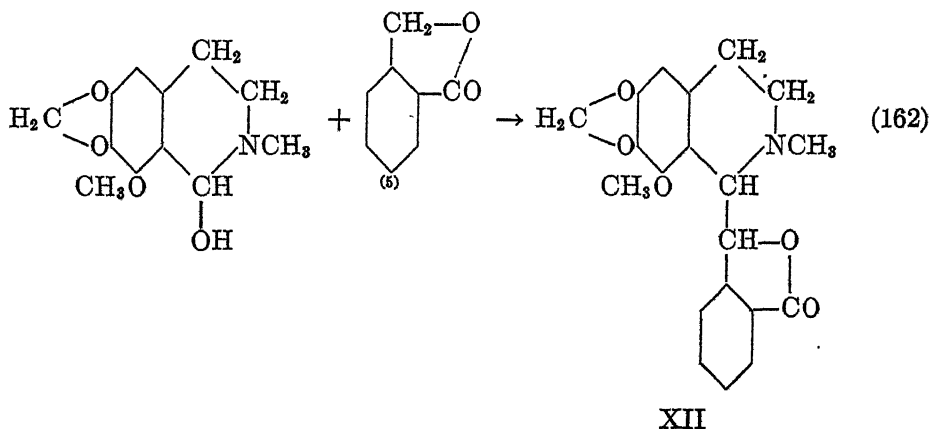
Anhydrocotarnine phthalide (XII) is an alkaloid, dedimethoxygnoscopine.

(*5*) One of the first condensations with cotarnine was carried out in 1887 by Bowman (83), who refluxed it with acetic anhydride to form an open-chain compound (V), by a Perkin-type reaction combined with an acetylation.

$$\text{XIII structure} + (CH_3CO)_2O$$

$$\text{structure} + H_2O \quad (163)$$
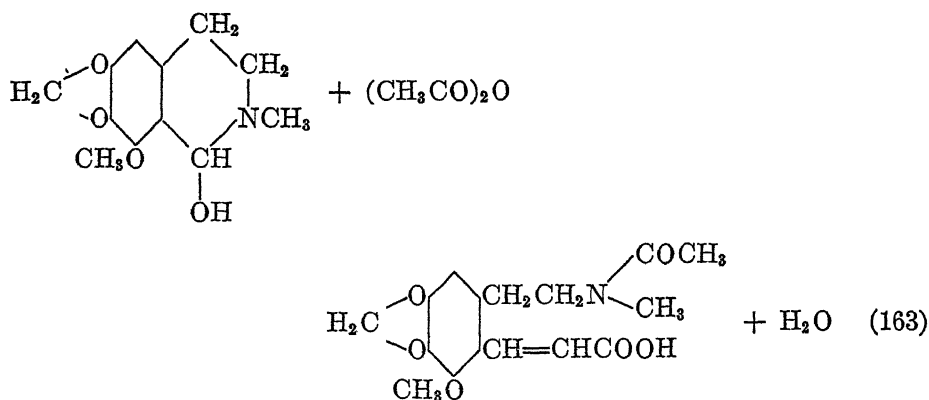
XIII

(6) With anhydrous hydrogen cyanide, cotarnine gives cyanohydro cotarnine (XIV), which exists in the equilibrium forms shown (189, 330, 410, 411):

$$C_8H_6O_3 \text{ structure}$$

XIV   XV
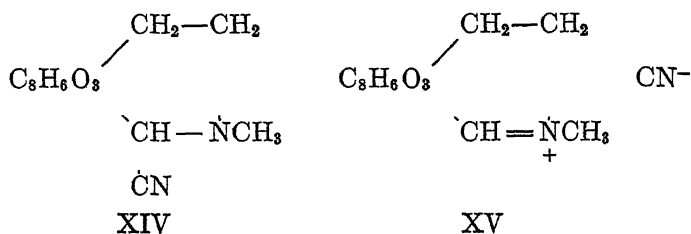
J. HYDRASTININE

Hydrastinine (II) (for constitution, see reference 252) bears the same relation to hydrastine (I) that cotarnine bears to narcotine.
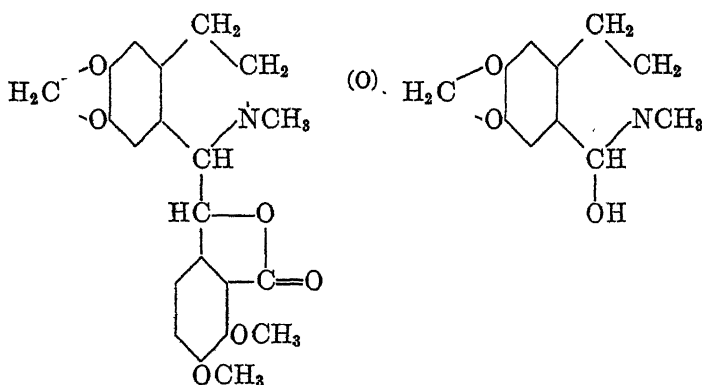
II

Hydrastinine may be formed by oxidizing hydrastine (344a, 344b, 749), by the action of alkali on its salts (187; cf. formula VII in equation 159), or by ring-closure methods (187, 205). The chemical similarity to cotarnine is very marked, as will be seen in the following examples:

(1) Hydrastinine reacts with nitromethane in boiling methanol to give anhydrohydrastinine nitromethane; a similar reaction occurs with 2,4-dinitrotoluene (437; cf. equation 160).

(2) Hydrastinine chloride reacts with ethylmagnesium bromide in ether to form 1-ethylhydrohydrastinine, in accordance with the equation (340):

$$Cl^- + C_2H_5MgBr \rightarrow$$

$$+ MgBrCl \quad (164)$$
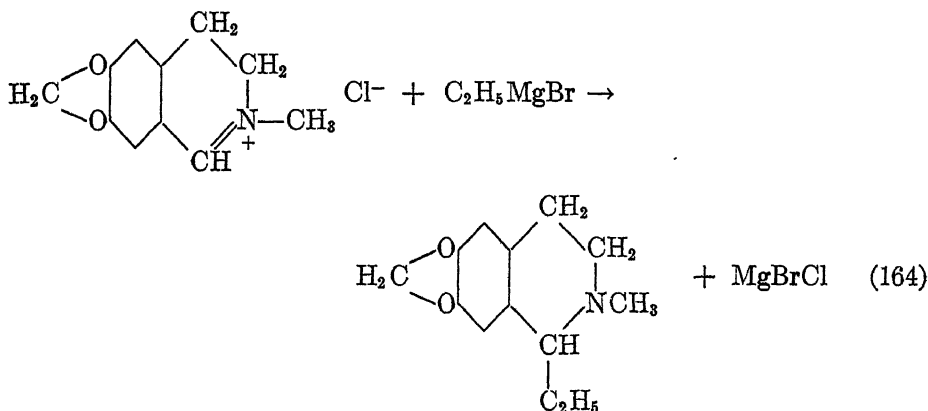
(3) Hydrastinine may be oxidized to oxyhydrastinine (IV), a cyclic ammono aquo ester (hydrastinic acid is also formed) (329, 339), and reduced to hydrohydrastinine (III), a cyclic ammono ether (34, 326, 336, 342, 344b). Simultaneous oxidation and reduction can be brought about by heating with alkali, in the sense of the Cannizzaro reaction (327, 343, 569; cf. 726), to give hydrohydrastinine and oxyhydrastinine.
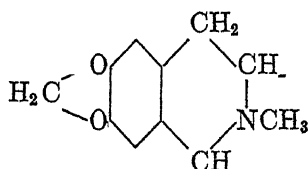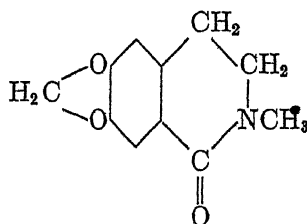
III   IV
Hydrohydrastinine   Oxyhydrastinine

(4) Hydrastinine condenses with acetone or with acetophenone in the presence of sodium carbonate to form anhydrohydrastinine-acetone or -acetophenone, respectively (560). Similar reactions occur with cumaron, malonic ester, and phenylacetic ester (563).

(5) Hydrastinine, boiled for 2 hr. with acetic anhydride under reflux, gives an open-chain compound (328), in a reaction of the type shown in equation 163.

(6) 3-Methylhydrastinine is reported to undergo condensations with greater facility than hydrastinine itself (640b).

VI. APPENDIX: THE REACTIVITY OF AMMONO AQUO ACETALS
AND OF AMMONO AQUO MEROACETALS

Aquo hemiacetals or their vinylogues (see xanthydrol, Section III), and the ammono aquo meroacetals, or "partial acetals" of the general formulas

$$RCH\begin{cases} OH \\ OR' \end{cases} \quad RCH\begin{cases} OH \\ NHR' \end{cases} \quad RCH\begin{cases} OH \\ NR_2' \end{cases} \quad RCH\begin{cases} OR' \\ NH_2 \end{cases} \quad RCH\begin{cases} OR' \\ NHR'' \end{cases}$$
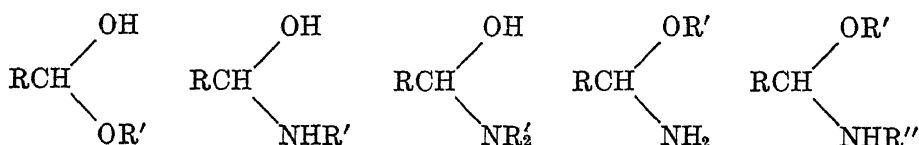
all have a reactivity comparable to or perhaps even exceeding that of typical open-chain aldehydes. The cyclic ammono aquo meroacetals, which include the pseudo bases of the pyridine, quinoline, and isoquinoline series, have been described in some detail previously (see Sections II, I, 7; IV, N, 2; V, G, 1). The following brief account of the properties of some of the open-chain compounds whose formulas are given above is for purposes of comparison.

A. MEROACETALS AND ACETALS AS POSSIBLE INTERMEDIATES IN THE KNOEVENAGEL AND MANNICH REACTIONS

1. The Knoevenagel reaction

The Knoevenagel reaction is the name applied to the ammonia- or amine-catalyzed condensation of an aldehyde with a compound having a reactive methylene group. Typical examples are given in the equations that follow:

$$C_6H_5CHO + CH_2(COOH)_2 \xrightarrow[50-70°C.]{NH_3} C_6H_5CH{=}C(COOH)_2 + H_2O \quad (165)$$
$$I$$

$$C_6H_5CHO + CH_2(COOH)_2 \xrightarrow[100°C.]{NH_3 \text{ or amines}}$$
$$C_6H_5CH{=}CHCOOH + CO_2 + H_2O \quad (166)$$
$$II$$

$$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow[heat]{NH_3 \text{ or amines}}$$
$$C_6H_5CH{=}C(COOC_2H_5)_2 + H_2O \quad (167)$$
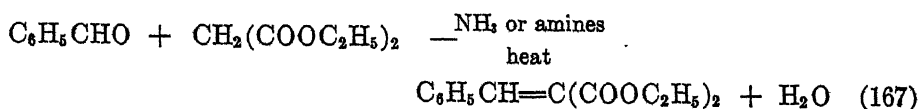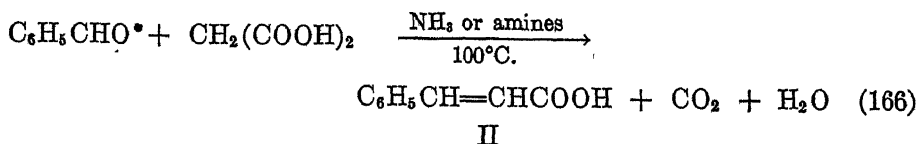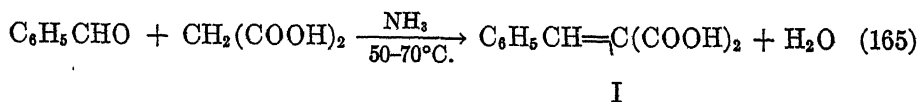
(References: equation 165, (478d); equation 166, (478b, 478d); equation 167, (478c)). The mechanism of this synthesis is not yet clear in all of its details, in spite of the large number of papers that have appeared upon this subject within recent years (14, 73c, 83b, 181b, 243a, 404a, 478a, 478b, 519c, 547b, 565c, 715b, 723a, 766a, 819b).

According to an earlier view of Knoevenagel (478a, 478b), the amine or ammonia used as a catalyst reacts with the aldehyde to form highly active inter-

mediate compounds (ammono acetals), as shown in the equations below, and these are responsible for the condensations observed.

$$C_6H_5CHO + 2C_5H_{10}NH \text{ (piperidine)} = H_2O + C_6H_5CH(NC_5H_{10})_2 \quad (168)$$
$$\text{III}$$

$$C_6H_5CHO + C_6H_5NH_2 = C_6H_5CH{=}NC_6H_5 + H_2O \quad (169)$$
$$\text{IV}$$

$$C_6H_5CH(NC_5H_{10})_2 + CH_2(COOH)_2 =$$
$$C_6H_5CH{=}CHCOOH + CO_2 + 2C_5H_{10}NH \quad (170)$$

$$C_6H_5CH{=}NC_6H_5 + CH_2(COOH)_2 =$$
$$C_6H_5CH{=}CHCOOH + CO_2 + C_6H_5NH_2 \quad (171)$$
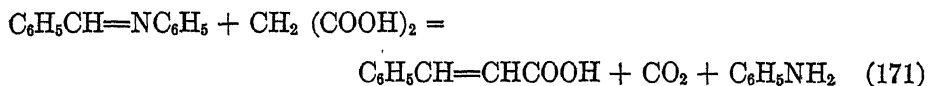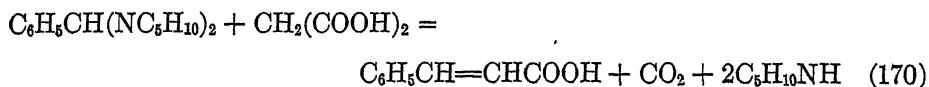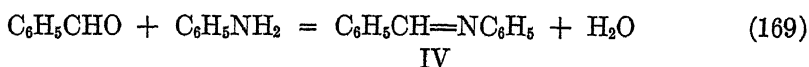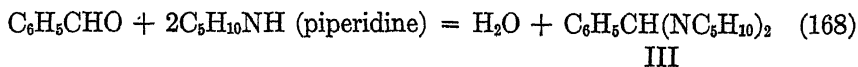
Knoevenagel (478b) has, in fact, carried out many reactions similar to those of equations 170 and 171, and has even found that hydrobenzamide condenses with malonic acid when heated in alcoholic solution, in the manner shown below:

$$(C_6H_5CH{=}N)_2CHC_6H_5 + 3CH_2(COOH)_2 =$$
$$3CO_2 + 2NH_3 + 3C_6H_5CH{=}CHCOOH \quad (172)$$
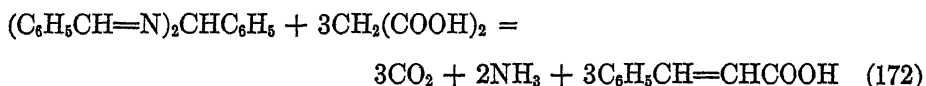
This method for preparing benzalmalonic acid (I) has recently been recommended by Boehm and Grohnwald (77b).

The Knoevenagel reaction is considered by Rodionov and his coworkers (715b; cf. 723a) to proceed in accordance with the following equations:

$$RCHO + NH_3 \rightarrow RCH{\Large\langle}{}^{OH}_{NH_2}$$
$$V$$

$$RCH{\Large\langle}{}^{OH}_{NH_2} + CH_2(COOH)_2 \rightarrow RCH(NH_2)CH(COOH)_2 + H_2O \quad (173)$$
$$V \qquad\qquad VI \qquad\qquad VII$$
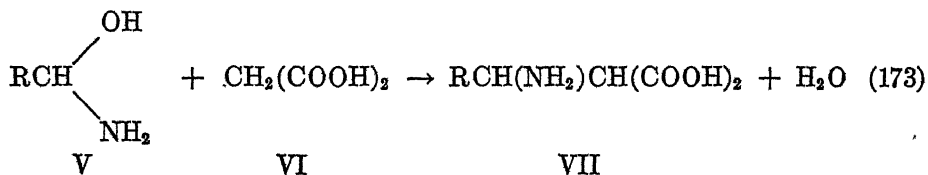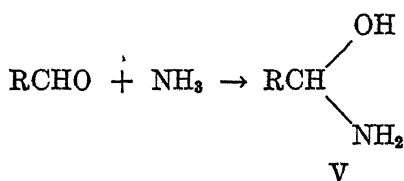
Subsequently the following reactions may occur:

$$VII \rightarrow RCH(NH_2)CH_2COOH + CO_2$$
$$VII \rightarrow RCH{=}CHCOOH + CO_2 + NH_3$$
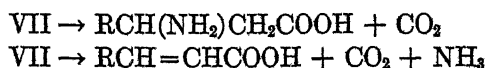
The ammonia may be replaced by a primary amine (e.g., CH_3NH_2) or by a secondary amine (such as piperidine) and malonic ester, $CH_2(COOC_2H_5)_2$, or a substituted malonic ester, $RCH(COOC_2H_5)_2$, may be used in place of the malonic

acid. It is accordingly possible to prepare compounds similar to those whose formulas are given below:

$$C_6H_5\,CH \Big\langle {}^{NH_2 \cdot HCl}_{C(COO\,C_2H_5)_2} \atop \underset{CH_3}{|}$$

VIII

$$C_6H_5\,CH(NC_5H_{10})\,CH \Big\langle {}^{COOH}_{COOH}$$

IX
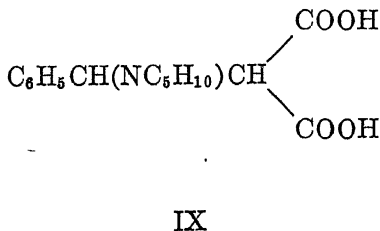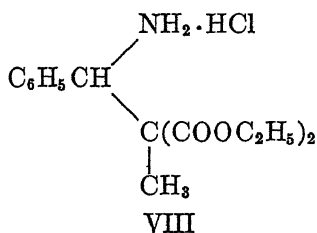
$(C_5H_{10}N-$ is the N-piperidyl radical).

An ammono aquo aldehyde solvate, $C_6H_5CH(OH)NH_2$, or the ammono aquo meroacetals, $C_6H_5CH(OH)NHCH_3$ and $C_6H_5CH(OH)NC_5H_{10}$, have therefore been regarded as intermediates in the reactions of equation 173 ($R = C_6H_5$).

The bearing of this work upon the mechanism of the Knoevenagel reaction must, however, await an answer to the objections that have been raised by Boehm and Grohnwald (77b). It is claimed that the compound prepared by the action of alcoholic ammonia on a mixture of malonic acid and benzaldehyde is the monoammonium salt of benzalmalonic acid,

$$C_6H_5\,CH{=}CH \Big\langle {}^{COOH}_{COONH_4}$$
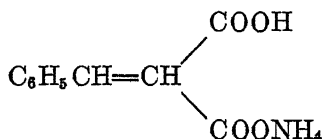
and not the aminobenzylmalonic acid (equation 173, formula VII, $R = C_6H_5$) that Rodionov thought he had prepared. Phenylaminopropionic acid, $C_6H_5CH(NH_2)CH_2COOH$, may be obtained by heating monoammonium benzalmalonate with dilute alcohol, evaporating the solvent, and treating the residue with hydrochloric acid, making it unnecessary to assume that the aldehyde derivative (V of equation 173) is an intermediate in its formation. Boehm and Grohnwald accordingly are of the opinion that the ammonia or amine is merely an enolization catalyst, but they do not seem to have explained satisfactorily the formation of the aminomalonic esters represented by formula VIII.

Hope and Robinson (435) believe that an addition compound of a secondary amine and an aldehyde, $R'CH(OH)NR_2$ (cf. equation 173), in the form of the true base $(R'CH{=}NR_2)OH$, is the effective intermediate in the Knoevenagel reaction (see Section IV, N, 2, b and reference 715a).

Because of the fact that tertiary amines are often very good catalysts (cf. 83b), the theory of an intermediate compound has been discarded by many investigators (73c, 83b, 181b, 404a, 519c, 547b, 819b), who believe that the function of the catalyst is to promote the enolization of the substance with reactive methylene. There follows an aldol-type condensation, with subsequent loss of water to give the unsaturated compound characteristic of the Knoevenagel reaction (cf. equation 173). It is assumed by some that the nitrogenous products so often isolated

are formed by the reaction of the amine catalyst with the intermediate aldol, but this view is not yet adequately supported experimentally.

Kuhn and coworkers (547b) have made the observation that piperidine will not catalyze the self-condensation of crotonaldehyde, though a small quantity of a salt of piperidine, such as the crotonate or acetate, will. They are therefore in agreement with the suggestion of Blanchard, Klein, and MacDonald (73c) that the Knoevenagel reaction is an example of positive-ion catalysis. Cope (181b) has recently found that acetamide, urea, piperidine, and ethylenediamine (but not sodium acetate) are good catalysts in acetic acid solution, and the results have been interpreted from the point of view of the extended Brönsted theory. It is considered that the function of the catalyst is to promote the enolization of the compound containing the reactive methylene group.

Even though an amine and an aldehyde may unite reversibly to give a reactive addition compound, $RCH(OH)NR_2'$ (equation 173), free aldehyde is still present and may well be the true intermediate in the Knoevenagel reaction (766a).

When primary amines are used as catalysts, it is probable that Schiff bases (X) are formed in the manner of the equation:

$$C_6H_5CHO + C_6H_5NH_2 \rightarrow C_6H_5CH{=}NC_6H_5 + H_2O \qquad (174)$$
$$X$$
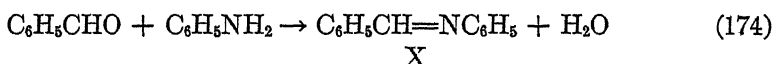
Worrall (819b) is of the opinion that the function of the Schiff base is to furnish, by hydrolytic reversal of the above reaction, a small amount of the primary amine which will then act as a catalyst in the usual way. The Schiff base, benzalaniline (X), is assumed to behave as shown below in the reaction of benzaldehyde, aniline, and nitromethane.

$$C_6H_5CH{=}NC_6H_5 + CH_3NO_2 \rightarrow C_6H_5CHNHC_6H_5 + H_2O$$
$$|$$
$$CH_2NO_2$$
$$X \qquad\qquad XI$$

$$XI + C_6H_5CHO \rightarrow C_6H_5CH{=}CHNO_2 +$$
$$XII$$

$$C_6H_5CH{=}NC_6H_5 + H_2O \qquad (174a)$$
$$X$$
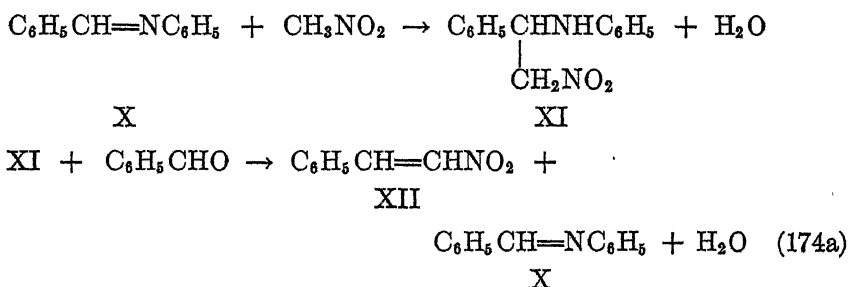
The first step is an aldol-like condensation of nitromethane with the ammono aldehyde ether, benzalaniline; presumably this must be catalyzed in the same manner as the corresponding reaction with benzaldehyde itself. The phenyl-aminonitroethylbenzene (XI) probably loses aniline to give the nitrostyrene (XII), and the former reacts with benzaldehyde to regenerate the Schiff base.

It is difficult to account satisfactorily for the observations of Boxer and Linstead (83b) that a β,γ-unsaturated acid is apparently the normal product of the condensation of butyraldehyde and malonic acid in the presence of tertiary amines.

$$CH_3CH_2CH_2CHO + CH_2(COOH)_2 \rightarrow$$

$$CH_3CH_2CH{=}CHCH_2COOH + CO_2 + H_2O \qquad (175)$$
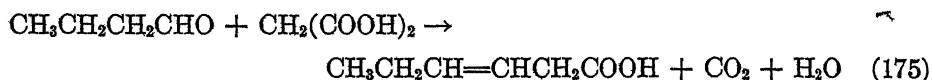
2-Hexenoic acid, $CH_3CH_2CH_2CH=CHCOOH$, is formed when a sufficient quantity of pyridine is used as a catalyst.

2. The Mannich reaction

The Mannich reaction consists in the condensation of formaldehyde and ammonia, a primary or secondary amine (usually as the hydrochloride) with a compound containing at least one reactive hydrogen (74). A typical preparation is the following (576a):

$$(CH_3)_2NH + CH_2O + CH_2(COOH)_2 \xrightarrow{0°C.}$$
$$(CH_3)_2NCH_2CH(COOH)_2 + H_2O$$

$$(CH_3)_2NCH_2CH(COOH)_2 \xrightarrow{heat}$$
$$(CH_3)_2NH + CH_2=CHCOOH + CO_2 \quad (176)$$
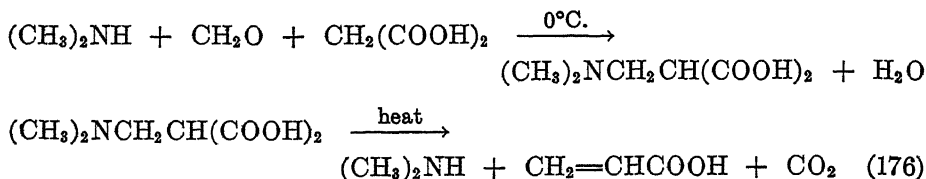
The products formed in a Mannich reaction are often of comparative instability and pass into unsaturated compounds, particularly when heated. The Knoevenagel synthesis (compare equation 173) is closely related, and the reaction under consideration here may likewise involve an intermediate product of addition of the amine to formaldehyde, $CH_2(OH)NR_2$. Doubt has been expressed as to whether this is the case, since antipyrine and dimethylaminomethanol, $(CH_3)_2NCH_2OH$, give a poorer yield of condensation product than antipyrine, formaldehyde, and the amine or amine hydrochloride (74a).

Heou-Feo Tseou (288c) is of the opinion that the dialkylaminomethanol, $CH_2(OH)NR_2$, or ammono aquo meroacetal, is an intermediate in the reaction between formaldehyde, a secondary amine, and quinaldine (see equation 99). An alternate possibility that the methylols,

$$C—CH_2CH_2OH$$
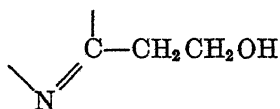
have a function in the synthesis has been disproved (288c; cf. 74a). It is believed that the instability of the dialkylaminomethanols is responsible for the failure to duplicate the yields of product that are obtained when an amine and formaldehyde react with quinaldine or other compound with reactive methyl or methylene.

B. REACTIVITY OF THE ISOLATED AMMONO AQUO MEROACETALS OR ACETALS

(1) McLeod and Robinson seem to have been the first to describe a reaction between an ammono aquo acetal and a compound with reactive hydrogen (570); two are given below:

$$CH_2 \begin{cases} N(C_2H_5)_2 \\ \\ OC_4H_9(i) \end{cases} + CH_3COC_6H_5 \rightarrow$$

$$i\text{-}C_4H_9OH + (C_2H_5)_2NCH_2CH_2COC_6H_5 \quad (177)$$

$$CH_2 \begin{cases} N(C_2H_5)_2 \\ \\ OC_5H_{11}(i) \end{cases} + CH_3C_6H_3(NO_2)_2\text{-}1,2,4 \rightarrow$$

$$i\text{-}C_5H_{11}OH + (C_2H_5)_2NCH_2CH_2C_6H_3(NO_2)_2 \quad (178)$$
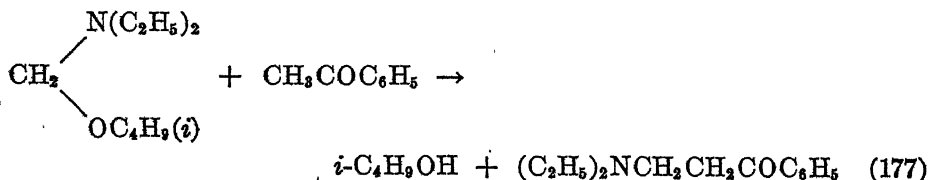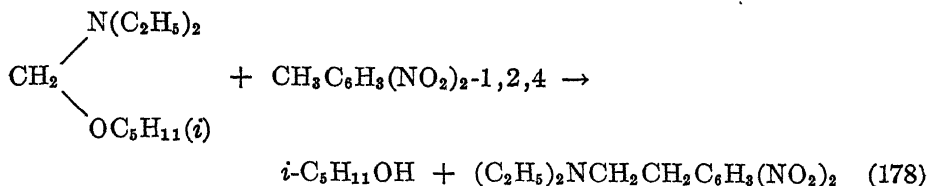
Tseou Heou-Feo and Yang (290) report reactions of the following type. No heating is required.

$$+ C_2H_5OCH_2NC_5H_{10} \rightarrow + C_2H_5OH \quad (182)$$
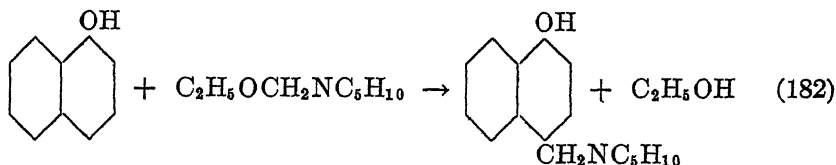
$C_5H_{10}N-$ is N-piperidyl.

(2) Stewart and Bradley (777; cf. 570) have found that the dialkylaminomethanols, R_2NCH_2OH, are very readily hydrolyzed under acid conditions.

(3) Phenols react with formaldehyde in the presence of ammonia or various amines to form bakelite-type resins. Ammono aquo meroacetals, $CH_2(OH)NR_2$, may possibly be intermediates, since formaldehyde, phenol, and dimethylamine are reported to react to give o-hydroxybenzyldimethylamine, o-$HOC_6H_4CH_2N$-$(CH_3)_2$ (233).

C. VINYLOGUES OF AMMONO AQUO ACETALS OR MEROACETALS

The high reactivity of these compounds often persists when two portions of the molecule are separated by one or more vinylene groups, as in the following examples:
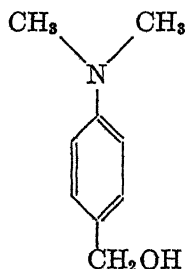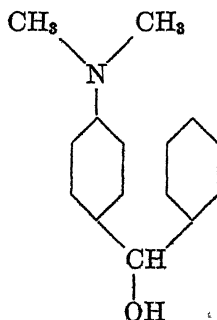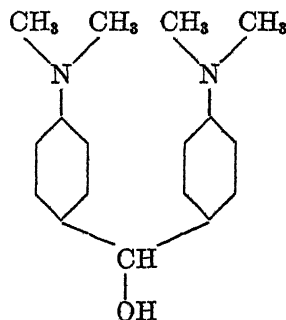
XIII   XIV   XV

Smith and Welch (766a) have prepared p-dimethylaminobenzyl alcohol (XIII) by condensing formaldehyde with dimethylaniline in the presence of concentrated hydrochloric acid. When phenol is heated with the dimethylaminobenzyl alcohol at 155–170°C., with the addition of a small quantity of triethylamine, 4-hydroxy-4′dimethylaminodiphenylmethane is formed in accordance with the equation:

$$(CH_3)_2NC_6H_4CH_2OH + C_6H_5OH = H_2O + (CH_2)_2NC_6H_4CH_2C_6H_4OH \quad (180)$$

p-Dimethylaminobenzohydrol (XIV) and bis(p-dimethylaminophenyl)carbinol (XV; Michler's hydrol) both condense with compounds having active hydrogen, in the sense of equation 180; many of these reactions have been patented. It must be admitted that benzohydrol, $(C_6H_5)_2CHOH$, will behave similarly, so no proper estimate can be made of the activating effect of the p-dialkylamino group on the hydroxyl, particularly since much of the earlier literature in this field is practically devoid of experimental data (318a, 318b, 318c, 318d, 318e).

It is interesting that the dimethylamino group of 1-dimethylamino-3-butanone (XVI) and the cyclohexanone derivative (XVII) can be replaced by residues of acetoacetic and malonic esters in the presence of sodium ethylate (576, 581; $cf.$ 574).

$$CH_3COCH_2CH_2N(CH_3)_2 \; + \; CH_2(COOC_2H_5)_2 \; \xrightarrow{\;NaOC_2H_5\;}$$
$$\text{XVI}$$

$$CH_3COCH_2CH_2CH(COOC_2H_5)_2 \; + \; (CH_3)_2NH$$

$$+ \; CH_3COCH_2COOC_2H_5 \; = \; (CH_3)_2NH \; +$$

(181)
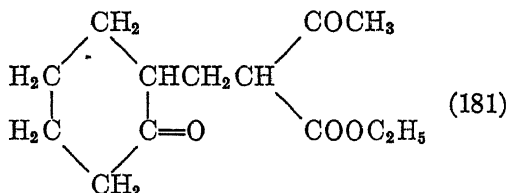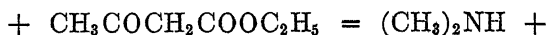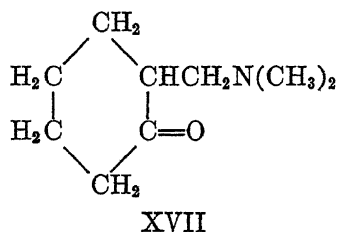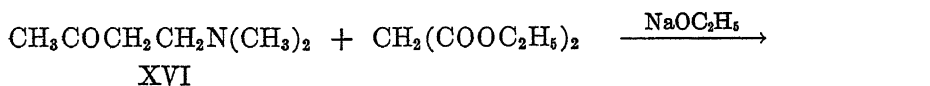
Both of the dimethylamino ketones above, in their tautomeric forms, contain the system,
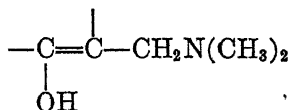
and so may be regarded as vinylogues of the ammono aquo meroacetal, $CH_2OHN(CH_3)_2$.

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CONVERSION OF HYDROCARBONS INTO BUTADIENE[1]

GUSTAV EGLOFF AND GEORGE HULLA

Universal Oil Products Company, Chicago 4, Illinois

CONTENTS

I. INTRODUCTION

Production of synthetic rubber is one of the outstanding scientific and industrial achievements in the war effort. U. S. production will be at the rate of over 1,000,000 tons annually toward the end of 1944. This is the result of intense co-operation of chemists and chemical engineers. Butadiene is one of the key hydrocarbons in the synthetic rubber industry. The present study covers the use of hydrocarbons as source material for the production of butadiene and also notes both experimental and theoretical work on the subject. It is hoped that the ideas submitted will be useful in connection with further development of the synthetic rubber industry.

Ostromyslenskiĭ in 1913 expressed the opinion that butadiene is obtainable from any organic compound by thermal treatment alone (118). He supported his statement with a list of twenty-one methods for preparing alkadienes, principally butadiene. Our study to date indicates that over eighty-five distinct organic reactions yield butadiene.

Many types of organic compounds have been converted into butadiene (31): alkanes, alkenes, alkadienes, alkynes, cyclanes, cyclenes, aromatics, haloalkanes, haloalkenes, halocyclanes, alkanols, alkenols, alkanals, alkenals, hydroxycyclanes, hydroxybenzenes, dialkyl ethers, alkyl alkenyl ethers, dialkenyl ethers, cyclic oxides, alkanoic acids, alkenoic acids, mono-, di-, and tri-esters, alkenyl sulfides, amines, piperidine, and organic ammonium derivatives. Natural and cracked gases, crude oil and its fractions, natural rubber, "butadiene rubber," and coal also yield butadiene upon thermal treatment. Apparently any petroleum or its products can be converted into butadiene (12, 96).

From the scientific standpoint, the optimum conditions for maximum yields of butadiene and underlying reaction mechanisms for some of the foregoing hydrocarbons are attractive fields for research. From the viewpoint of national defense and economy, petroleum and natural gas are logical sources for the production of many types of unsaturated hydrocarbons (44).

Although butadiene is generally taken to be the only C_4H_6 hydrocarbon produced, careful work is expected to show the presence of at least traces of butadiene-1,2, butyne-1, and butyne-2. Butadiene in this study means the 1,3 or conjugated isomer. The isomers of butadiene-1,3, being more reactive, probably polymerize or decompose or are present in such small percentages that they have not been reported. Highly specific tests for small percentages of isomers in samples of butadiene-1,3 are lacking but are nevertheless desirable.

II. INDIVIDUAL HYDROCARBONS

A. ALIPHATIC SERIES

1. Alkanes

a. Thermal conversion

Nine lower alkanes are known to yield butadiene upon thermal treatment at 500–950°C.: methane (63), ethane (64), ethane + propane (17, 163), propane (15, 55, 64), propane + butane (161, 162), propane + butane + pentane (131), n-butane (55, 64, 76), 2-methylpropane (76), n-pentane (14, 108, 113), 2-methylbutane (14), n-hexane (64, 113, 124), and 2-methylpentane (113). The lower-molecular-weight members, e.g., methane, require the highest temperatures. The yields reported in all cases are low, less than 5 per cent on feed per pass, indicating a need of additional experiments to establish guiding principles. Butadiene from hydrocarbons is a reaction product of relatively high temperatures. Its heat of formation is −26 kcal. per gram-mole at 18°C., comparable to −53.9 kcal. for ethyne. Consequently, some of the techniques used in the production of ethyne, such as rapid cooling of reaction products from the electric-arc treatment of hydrocarbons, may be applied in the case of butadiene.

Electric-arc treatment of alkane gases or vapors also yields butadiene, as in the cases of methane (153), and n-hexane, n-heptane, n-octane, n-nonane, and n-decane (127). The high temperature of the electric arc relates these conversions to the corresponding thermal treatments. All auxiliary or electrical effects, such as enhanced ionization, polarizations, or radiation, are elusive and may not exist (154).

Theory concerning the thermal decomposition of alkanes may be said to begin with the work of Haber on n-hexane (59, 60, 61). He contended that the primary decomposition of n-hexane and similar alkanes was scission of the molecule into methane and the complementary alkene. Ostromyslenskiĭ's views were probably greatly influenced by the foregoing study. In explaining the formation of butadiene from alkanes, this experimenter proposed the following equation (124):

$$RC_4H_8R' \rightarrow CH_2=CH-CH=CH_2 + RH + R'H$$
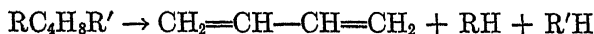
in which R and R' are alkyl groups. Demethanation of n-hexane was given as a specific example:

$$CH_2-CH_2-CH_2-CH_2 \longrightarrow CH_2=CH-CH=CH_2 + 2CH_4$$
$$\underset{CH_3}{|} \qquad\qquad \underset{CH_3}{|}$$
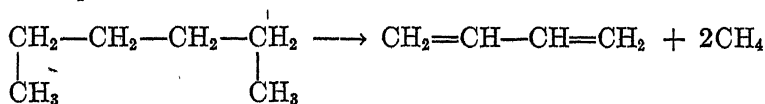
The general process was described as "liberation of RH (R being an alkyl) from straight chain saturated hydrocarbons regardless of their composition and structure." The words "straight chain" should not be taken too literally, because some branched-chain hydrocarbons were included. The statement apparently was intended to exclude cyclic hydrocarbons. Actually, the conversions were regarded as a sequence of two dealkanations (123, 124):

$$RC_4H_8R' \rightarrow RC_4H_7 + R'H$$

$$RC_4H_7 \rightarrow CH_2=CH-CH=CH_2 + RH$$
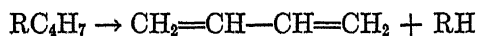
Accordingly, thermal degradation of n-hexane should give first methane plus pentene-1, and secondly, methane plus butadiene from the pentene.

Any extended explanation of butadiene formation in alkane pyrolysis must consider the rôle of primary decomposition. Hurd, disagreeing with Haber's belief that n-hexane first splits into methane and pentene, stated (69): "His data show that the chief unsaturated reaction product is propene and not amylene. Therefore, without proof to the contrary, one may question Haber's assertion that the amylene decomposed at once into propene and ethene. It seems reasonable to infer that propene was formed as a primary product."

Hague and Wheeler observed that dehydrogenation is less important in the decomposition of higher alkanes at lower temperatures (64). Demethanation of propane and n-butane exceeded the corresponding dehydrogenations. Also, the deëthanation of n-butane was greater than either its demethanation or its dehydrogenation at 650–700°C. These observations have probably influenced subsequent theories to a marked extent. For example, Frey has pointed out (53): "Paraffin hydrocarbons decompose chiefly into simpler complementary olefins and paraffins. High decomposition temperatures favor the concomitant formation of complementary olefins and hydrogen, and in some cases more than two hydrocarbon product molecules are formed. Two reaction mechanisms in accord with these observations have been proposed."

Types of primary decomposition were summarized by Frey as follows:

$$C_2H_6 \longrightarrow C_2H_4 + H_2$$

$$C_3H_8 \begin{cases} \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_3 + H_2 \\ \longrightarrow CH_2\!\!=\!\!CH_2 + CH_4 \end{cases}$$

$$n\text{-}C_4H_{10} \begin{cases} \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_3 + CH_4 \\ \longrightarrow 2CH_2\!\!=\!\!CH_2 + H_2 \\ \longrightarrow CH_2\!\!=\!\!CH_2 + C_2H_6 \\ \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_2\!-\!CH_3 \\ \qquad (\text{and } CH_3\!-\!CH\!\!=\!\!CH\!-\!CH_3) + H_2 \end{cases}$$

$$CH_3CH(CH_3)_2 \begin{cases} \longrightarrow CH_2\!\!=\!\!C(CH_3)_2 + H_2 \\ \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_3 + CH_4 \end{cases}$$

$$n\text{-}C_5H_{12} \begin{cases} \longrightarrow 2CH_2\!\!=\!\!CH_2 + CH_4 \\ \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_3 + C_2H_6 \text{ (or } C_2H_4 + H_2) \\ \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_2\!-\!CH_3 + CH_4 \end{cases}$$

$$(CH_3)_2CHCH_2CH_3 \begin{cases} \longrightarrow CH_3\!-\!CH\!\!=\!\!CH\!-\!CH_3 + CH_4 \\ \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_3 + C_2H_6 \\ \longrightarrow CH_2\!\!=\!\!CH_2 + C_3H_8 \\ \longrightarrow CH_2\!\!=\!\!C(CH_3)_2 + CH_4 \end{cases}$$

$$C(CH_3)_4 \longrightarrow CH_2\!\!=\!\!C(CH_3)_2 + CH_4$$

$$(CH_3)_2CHCH(CH_3)_2 \begin{cases} \longrightarrow (CH_3)_2C\!\!=\!\!CH\!-\!CH_3 + CH_4 \\ \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_3 + C_3H_8 \\ \longrightarrow 2CH_2\!\!=\!\!CH\!-\!CH_3 + H_2 \end{cases}$$

The rôle of secondary reactions in the formation of butadiene and more conjugated products (aromatics) has been considered by Frolich, Simard, and White (55). These workers suggest the following series of reactions to account for the formation of high-boiling compounds: (a) cracking of alkanes into alkenes, (b) formation of butadiene from pairs of alkene molecules, (c) formation of an aromatic from butadiene and an alkene (18), and (d) interaction of aromatics and alkenes to form heavier compounds. Butadiene was considered to be formed from ethene and propene, representing primary reaction products as follows:

$$2C_2H_4 \quad C_4H_6 + H_2$$
$$2C_3H_6 \quad C_4H_6 + C_2H_6$$
$$C_2H_4 + C_3H_6 \quad C_4H_6 + CH_4$$
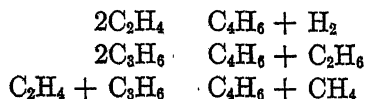
Frey has also considered the rôle of hydrogen migration in the thermal decomposition of alkanes, including the mechanism of transfer of a hydrogen atom from the carbon atom one removed from the fracture point to the other fragment formed (53). The possibilities include a dissociation into alkyl radicals, one of which acquires a hydrogen atom from the other (68), and a semi-ionization process whereby one radical may transfer its allegiance to the hydrogen atom of the other radical (13). Kassel has suggested that the decomposition may involve formation of alkane and alkylidene, the latter rearranging to alkene (85), or formation of three molecules without the formation of free alkyl radicals (86). For example, n-butane would form one hydrogen and two ethene molecules if two hydrogen atoms at opposite ends of the carbon chain come into proximity. n-Pentane would yield methane instead of hydrogen.

Schmidt has formulated a double-bond rule, maintaining that the double bond between two carbon atoms strengthens the adjacent single bonds and weakens the next following (139). The mechanism of bond scission was later considered from the electronic standpoint (140). Cracking of alkanes was explained in the following way (140):

"The first reaction is the formation of a double bond by the splitting-off of two hydrogen atoms. The location of the double bond is then decisive for the location of rupture. This hypothesis is not the customary one. Heretofore it has been assumed that the breaking of a bond between two carbon atoms is the first step in the cracking reaction. . . .

"In cracking aliphatic hydrocarbons, the scission in which chains of three carbon atoms are formed is favored (139). Using the double bond rule, we assume that the first step of the cracking process is the formation of a double bond in position 1:2, by splitting off two hydrogen atoms in the same position and find:

$$CH_3-CH_2-CH_2-CH_2-CH_2-CH_3 \rightarrow CH_2=CH-CH_2-CH_2-CH_2-CH_3 + H_2."$$
$$\downarrow$$
$$CH_2=CH-CH_3 + CH_3-CH_2-CH_3$$
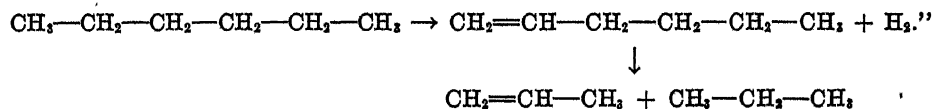
Staudinger, however, antedates Schmidt in pointing out the weakness of β-bonds in general, e.g., alkyl compounds and grouping were extensively considered (146, 147, 149, 150).

Since n-hexane produces butadiene upon thermal treatment at 500–900°C. (64, 113, 124), Schmidt's explanation must be amended. The production of butadiene can be ascribed either to scission of hexene-2 or to conversion of propane and/or propene. The former appears more probable:

$$CH_3-CH=CH-CH_2-CH_2-CH_3 \rightarrow CH_3-CH=CH-CH_3 + CH_2=CH_2$$

or

$$CH_3-CH=CH-CH_2-CH_2-CH_3 + H_2 \rightarrow CH_3-CH=CH-CH_3$$
$$+ CH_3-CH_3$$
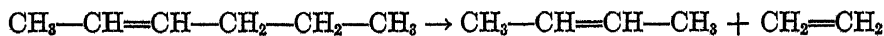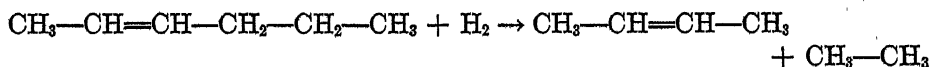
Dehydrogenation of butene-2 would then produce butadiene.

Kassel stated that it appears possible to give a nearly complete account of the decomposition reactions of organic chemistry in terms of 1,1, 1,2, and 1,4

unsaturation (86). Referring to the usual 1,4 reactions involving a system of conjugated double bonds between carbon atoms and with retrospect to the views (49) of Eyring, Sherman, and Kimball on the addition of hydrogen or bromine to butadiene, Kassel writes:

"There is also a second possible type of 1:4 dehydrogenation:

$$CH_3CH_2CH_2CH_3 \rightarrow H_2 + CH_2=CH_2 + CH_2=CH_2$$
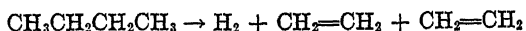
This type actually corresponds somewhat more closely to the six-electron model than does the production of butadiene from butylene. It is approximately 20 kcal. more endothermic, however, since it takes more energy to break C—C than it does to reduce C=C to C—C. The difference in activation energy will be considerably less than 20 kcal.; accurate predictions are impossible, but it appears worth while to look for this type of decomposition of hydrocarbons with a straight chain of at least four carbon atoms. By analogy with the 1:2 case, we shall expect to find 1:4 loss of methane, ethane, etc."

Referring back to Frey's types of primary decomposition for alkanes and taking into account the established thermal dehydrogenations (7, 14, 51, 107, 111, 155, 158) of butene-1, cis-butene-2, and trans-butene-2 into butadiene, the last hydrocarbon may be a secondary product from such alkanes as n-butane, n-pentane, and 2-methylbutane. Thermal condensation of ethene (52, 63, 110, 114, 138, 142, 144, 155, 157, 158, 164) also yields butadiene, so that the latter could be a secondary or tertiary product from ethane, propane, n-butane, n-pentane, and 2-methylbutane. Whenever ethene dehydrogenates to vinyl radicals and then condenses, butadiene is a secondary product. But the polymerization of ethene into a straight-chain butene, followed by the latter's dehydrogenation, gives the same diene as a tertiary product from the alkane (ethane, propane, n-butane, 2-methylpropane, n-pentane, and 2-methylbutane). Finally, in order to obtain butadiene from 2-methylpropene, i.e., as a tertiary product in the "decomposition" of 2-methylpropane, 2-methylbutane, or tetramethylmethane, it is necessary to isomerize the branched alkene into butene-1 or butene-2.

A theoretical approach not entirely different from the discussion on the rôle of primary decomposition is the a priori view afforded by a "new" theory. To keep the discussion in accordance with the writings of chemical physicists, we shall first consider the nomenclature of intact groups and isolated radicals, leaving all distinctions between groups and radicals to the text or reader. Organic nomenclature begins logically with the names of the large classes of hydrocarbons: namely, the alkanes, alkenes, alkadienes, alkynes, alkenynes, alkadiynes, cyclanes, cyclenes, bicyclanes, bicyclenes, and aromatics. Monovalent groups and radicals, which are formed respectively by replacement or loss of a hydrogen atom, are known generically as alkyl, alkenyl, alkadienyl, alkynyl, alkenynyl, alkadiynyl, cyclanyl, cyclenyl, bicyclanyl, bicyclenyl, or aryl groups and radicals. The names of specific groups and radicals retain the roots of individual hydrocarbon names, as shown in table 1. Divalent groups and radicals are named as diyls; poly-yls are encountered also.

In the case of specific groups and radicals, it is customary to assign definite

TABLE 1

Nomenclature of groups and radicals

RADICAL	NAME
Monovalent:	
$CH_2CH_2CH_2CH_3$	Butyl-1
$CH_3CHCH_2CH_3$	Butyl-2
$CH=CHCH_2CH_3$	But-1-en-1-yl
$CH_2=CCH_2CH_3$	But-1-en-2-yl
$CH_2=CHCHCH_3$	But-1-en-3-yl
$CH_2=CHCH_2CH_2$	But-1-en-4-yl
$CH_2CH=CHCH_3$	But-2-en-1-yl
$CH_3C=CHCH_3$	But-2-en-2-yl
$CH=CHCH=CH_2$	Buta-1,3-dien-1-yl
$CH_2C\equiv CCH_3$	But-2-yn-1-yl
$CH\equiv CCH=CH$	But-3-en-1-yn-4-yl
$C\equiv CC\equiv CH$	Buta-1,3-diyn-1-yl
H_2C\ $\quad$CH—$\quad$$H_2C$	Cyclopropyl
CH / H_2C CH / H_2C CH— / CH_2	Cyclohex-1-en-3-yl
Divalent:	
—$CHCH_3$	Ethane-1,1-diyl
CH_2CH_2	Ethane-1,2-diyl

TABLE 1—*Continued*

$CH_2CH_2CHCH_3$

Butane-1,3-diyl

$CH=CH$

Ethene-1,2-diyl

$CH=CHCH_2CH_2$

But-1-ene-1,4-diyl

$CH_2=CHCHCH_2$

But-1-ene-3,4-diyl

$CH_2C=CHCH_3$

But-2-ene-1,2-diyl

$CH_2CH=CHCH_2$

But-2-ene-1,4-diyl

$CH=CCH=CH_2$

Buta-1,3-diene-1,2-diyl

$CH=CHCH=CH$

Buta-1,3-diene-1,4-diyl

$$\begin{array}{c}CH-\\ H_2C \quad CH-\\ H_2C \quad CH_2\\ CH_2\end{array}$$

Cyclohexane-1,2-diyl

Polyvalent:
   $CH_2CHCHCH_3$

Butane-1,2,3-triyl

$CH_2CHCHCH_2CH_3$

Pentane-1,2,3-triyl

—$CHCH$—

Ethane-1,1,2,2-tetrayl

—$CHCHCH_2CH_2$

Butane-1,1,2,4-tetrayl

Ethanehexayl

electrical charges to the carbon atoms whose valencies are "exposed." Such carbon atoms are positive, neutral, or negative, according to whether they expose zero, one, or two electrons. The corresponding radicals are known as positive

ions, free radicals, and negative ions, respectively. Three kinds of methyl radicals, for example, could be considered:

$$\begin{array}{ccc}
\text{H} & \text{H} & \text{H} \\
\text{H:}\overset{..}{\text{C}}\text{:H} & \text{H:}\overset{..}{\text{C}}\text{:H} & \text{H:}\overset{..}{\text{C}}\text{:H} \\
\text{Positive ion} & \text{Free radical} & \text{Negative ion}
\end{array}$$

When a solid line instead of a designated number of electrons is used in structural formulas of radicals, it remains to be decided which of the three types of radicals is most probably present.

In the thermal treatment of hydrocarbons, including alkanes, alkenes, alkynes, and cyclanes, ethane is a reaction product (25, 46). Its formation can be taken as an indication of the presence of successive units of two carbon atoms in many hydrocarbons. The formation of ethyne can often be explained on the same basis. The basic cause of the aforesaid formation of ethene, ethyne, and butadiene in the thermal conversions of higher alkanes and alkenes or those containing more than four consecutive methylene groups is an inherent deficiency in alternate carbon–carbon bond strengths. Points of scission corresponding to weakness in bonds will be indicated by segmented lines, as in the following formula for a higher alkane:

We ascribe such deficiency in bond strengths mainly to shearing forces caused by the repulsion of hydrogen atoms facing each other, especially in *cis* structures:

Cis structures are probably formed whenever the aforesaid molecules are subjected to high rates of energy input under high-temperature conditions. Mixed *cis* and *trans* structures, of course, would prevail in the interim. In the two molecules depicted, X and Y represent inactive groups. They enclose an active chain of ethanediyls about to form ethene fragments ("C_2H_4 directive fragmentation"). The conditions under which fragments of butene, hexene, etc. are directly formed do not need to be considered now. The weak C—C bonds pre-

sumably would vie with the adjacent C—H bonds for additional attractive strength. Consequently, thermal dehydrogenation would center about initially weak C—C bonds and would there be competitive with chain scission. Double bonds formed by dehydrogenation would strengthen the linkage between all pairs of carbon atoms that lose hydrogen and would correspondingly further weaken the C—C bonds in the β-position so that scissions would occur:

Inspection of Fisher–Hirschfelder atom models indicates that the corresponding *trans* molecules would undergo scission also:

We shall call the over-all process a "C_4H_8 directive fragmentation."

b. Catalytic conversion

Alkanes may be converted in other ways than thermal treatment *per se*. Dehydrogenation of *n*-butane into butadiene can be conducted catalytically in several ways: one-stage catalysis (400–650°C.) and two-stage catalysis (482–650°C.). One-stage catalysis is a process requiring reduced pressure and short contact time (91). By a single passage, 12.2 weight per cent of butane was converted into butadiene with less than 0.2 per cent by weight of carbon. On recycling, 74 weight per cent of butadiene may be produced with the deposition of 2.3 weight per cent of carbon on the catalyst. The catalyst may be chromia (54) or else alumina supporting some chromia, molybdenum trioxide, or vanadium trioxide (58). Two-stage catalysis first forms butene-1 and butene-2, which are dehydrogenated in the second stage under subatmospheric pressure (79, 145, 156, 167):

$$CH_2{=}CH{-}CH_2{-}CH_3$$
$$CH_3{-}CH_2{-}CH_2{-}CH_3 \qquad\qquad CH_2{=}CH{-}CH{=}CH_2$$
$$CH_3{-}CH{=}CH{-}CH_3$$

Butadiene yields up to 67 per cent by weight of *n*-butane charge are obtainable in the recycling operation. It is desirable that the butenes entering the second stage be devoid of hydrogen and of unreacted *n*-butane. This facilitates the final dehydrogenation to butadiene. A catalyst is generally used in both stages.

In one butadiene process, heat generated during the regeneration of carbonized catalyst is utilized in the dehydrogenations. A heat balance is secured by adjusting the prevailing pressures (1, 2, 116). Pyrolysis at 680°C. over porcelain balls or quartz pieces in the presence of carbon dioxide can be employed alternatively in the second stage (79). The carbon dioxide atmosphere serves to decrease the partial pressure of the butenes and may possibly oxidize some of the hydrogen to water.

Balandin believes that an edgewise orientation of *n*-butane molecules about the active centers (atoms) of a chromia catalyst leads to formation of butene-1 and butene-2, followed by their interisomerization and only concluded by conversion of butene-1 into butadiene molecules (3). The several steps can be depicted as follows, using Balandin's models:

The upper two rows of structures represent conversions of *n*-butane (*cis* form oriented 1,2 or 2,3 as in A or B) into butene-1 (C) and butene-2 (D) on the surface of the catalyst. Active centers are designated by circles with dots. The parts of the molecule that do not enter into the catalysis are turned away from the catalyst. It will be observed in A, B, and also in E, which is a 3,4 orientation of butene-1, that an atom of the catalyst lies midway between two adjacent carbon atoms (large spheres) each of which loses a hydrogen atom (small sphere) before leaving the surface. Structures C and D represent 1,3 orientations of butene-1 and butene-2, respectively; these forms enable an allylic type of hydrogen migration (isomerization) to occur reversibly. This seems to be important, since it is maintained by Balandin that only butene-1, oriented as in E, can yield butadiene. Unfortunately, the spheres are poor representations of molecular systems comprising nuclei each separated by relatively great distances (8). However, the tetrahedral arrangement of valences is acceptable. The conflict with Schmidt's double-bond rule, whereby butene-1 should give propene plus methylene (eventually ethene), can be overcome by assuming that corresponding

"dislocating influences" are absent whenever the carbon atoms of the double bond orient themselves on active centers. Also, the lower temperatures used in catalytic dehydrogenation tend to make the reaction more specific: there is much less dependence on thermal activation of the molecule.

"Catalytic cracking" of 2-methylbutane over silica gel at 680°C. gave butadiene as a product (102a). The conversion temperature was 80°C. higher than that used for the thermolysis (14). Consequently, in the absence of comparable kinetic data, the catalytic activity of silica gel for demethanation plus dehydrogenation may be questioned. The substance may function largely as a heat transfer medium and to some extent as an aromatization catalyst.

2. Alkenes

A variety of reactions are available for the direct conversion of ethene into butadiene: namely, thermal treatment (33), electrical condensation in the presence or absence of ethyne (35), catalytic dehydrogenation over copper (37), partial oxidation in the presence of air, sulfur, ferric oxide, or ferric chloride (36, 37), and condensation with ethanediol-1,2 or ethyne (37). Thermal treatment has been extended to propene, butene-1, butene-2, 2-methylpropene, pentene-1, pentene-2, 3-methylbutene-1, 2-methylbutene-2, hexene-1, 3-methylpentene-1, 4-methylpentene-1, 2,4,4-trimethylpentene, and n-hexadecene (33). Catalytic dehydrogenation has been extensively applied to butene-1, butene-2, and their mixtures (36). A small amount of butadiene is formed in the catalytic cracking of butene-1 and butene-2 (45).

a. Ethene

The thermal conversion mechanism for ethene was summarized by Lurie as follows (101):

"It may be assumed that butene is first formed and this is dehydrogenated to butadiene. A different explanation consists in dehydrogenation of ethene to a vinyl radical which condenses with ethene, and the resulting radical is further dehydrogenated to butadiene. Experience shows that simpler conditions are required and higher yields of butadiene obtained when the process is carried out in two stages: at 250–300°, ethene is dimerized and this is followed by dehydrogenation of butene."

Dunstan, Hague, and Wheeler are exponents of a polymerization–dehydrogenation theory (23, 24, 65). They maintain that ethene polymerizes to butene and then dehydrogenates into butadiene (24).

The "different" explanation mentioned in Lurie's review is covered by that of Hurd (70):

"The bivalent radical from ethylene (listed below as CH_2—CH_2) may be expected to do two things as it comes in contact with unchanged ethylene molecules. It may appropriate hydrogen, a reaction leading to ethane and acetylene, or it may add to the double bond:

Reaction 1.

$$CH_2\!-\!CH_2 + CH_2\!\!=\!\!CH_2 \longrightarrow CH_3CH_2 + CH_2\!\!=\!\!CH\!-$$
$$\;\,|\quad\;\; |\qquad\qquad\qquad\qquad\qquad |$$

or

$$CH_2\!-\!CH_2 + 2CH_2\!\!=\!\!CH_2 \longrightarrow CH_3CH_3 + 2CH_2\!\!=\!\!CH\!-$$
$$\;\,|\quad\;\; |$$

"The addition reaction may be considered to have the following sequence:

Reaction 2.

$$CH_2\!-\!CH_2 \xrightarrow{\;CH_2=CH_2\;} CH_2\!-\!CH_2\!-\!CH_2\!-\!CH_2 \xrightarrow{\;CH_2=CH_2\;}$$
$$\;\,|\quad\;\; |\qquad\qquad\qquad |\qquad\qquad\qquad |$$
$$\text{A}$$

$$CH_2\!-\!CH_2\!-\!CH_2\!-\!CH_2\!-\!CH_2\!-\!CH_2, \text{ etc.}$$
$$\;\,|\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\text{B}$$

"Reaction 1 calls for higher temperatures than reaction 2. The univalent radical of (1) may add also to ethylene as in (2), but at their high temperature of formation it is to be expected that the greater part of the CH_3CH_2- and $CH_2=CH-$ radicals would change into C_2H_4 and C_2H_2, respectively, by detachment of a hydrogen atom. Some ethane would escape, but much of it would pyrolyze further into $2CH_3-$, thence into $2CH_4$ as in reaction 1 or into $2CH_3CH_2CH_2-$, etc., as in reaction 2. The product (2B) may isomerize to cyclohexane. Dehydrogenation of (A) and (B) would be brought about by collision with other radicals. Thus, (A) would give rise to butadiene and (B) to cyclohexene or benzene. The lower the temperature, the greater should be the tendency for a long polymeric chain."

Zanetti, Suydam, Jr., and Offner stated (164): "The direct formation of butadiene from ethylene takes place according to the equation, $2C_2H_4 \rightarrow CH_2=CH-CH=CH_2 + H_2$. It will be noted that there is no change of volume in this reaction, which means that the pressure in the reactor would have no influence on the quantity of butadiene formed."

Schneider and Frolich rejected the idea that butene is an intermediate in butadiene formation, because data extrapolated for zero per cent cracking showed about 41, 36, 12, and 3 moles of hydrogen, butadiene, propene, and butene, respectively, for each 100 moles of ethene reacting (142). Accordingly, about 72 per cent of the ethene reacting was considered to form butadiene plus hydrogen as initial products:

$$2C_2H_4 \rightarrow C_4H_6 + H_2$$

The following conclusions were part of those made in regard to the thermal cracking at 725°C. of propane, ethene, and propene:

"That cracking reactions are approximately first order and homogeneous is confirmed, even in those cases where the initial products formed point toward a dimolecular reaction. If anything, the order is even lower than first. Thus, while the initial products from both ethylene and propylene indicate that the main reactions are dimolecular, the amount of propylene reacting is actually increased threefold by lowering the concentration of the olefin from one to one-eighth atmosphere by dilution with an inert gas. Also in cracking ethylene,

where the main reaction is polymerization of two molecules with simultaneous elimination of hydrogen to form butadiene, it was found necessary to raise the temperature more than 25° in order to obtain the same percentage cracking at atmospheric pressure as that obtained at one-fifth atmosphere. In other words, instead of varying as the square of the pressure (as a simple dimolecular reaction should), the rate increased even less than the first power of the pressure. The absence of surface catalytic effects was shown by packing the cracking tube with broken quartz. As a matter of fact, the results indicate less cracking in a packed tube than in an open one.

"It has been established that higher hydrocarbons can be built up from lower ones otherwise than by simple polymerization. Examination of the initial products from the cracking of ethylene and propylene has shown the importance, not generally recognized hitherto, of reactions of the type,

$$2C_3H_6 \rightarrow C_2H_4 + C_4H_8$$

Other reactions of this type which have been shown to take place are:

$$2C_2H_4 \rightarrow C_4H_6 + H_2$$
$$2C_3H_6 \rightarrow C_2H_6 + C_4H_6$$
$$C_2H_4 + C_4H_6 \rightarrow C_6H_8 + H_2$$
$$C_2H_4 + C_4H_6 \rightarrow C_6H_6 + 2H_2$$

And still others indicated but not definitely proved are:

$$2C_3H_8 \rightarrow C_2H_6 + C_4H_{10}$$
$$2C_3H_6 \rightarrow C_6H_{10} + H_2$$
$$2C_3H_6 \rightarrow C_5H_8 + CH_4$$

"Reactions of this type may be explained satisfactorily on assumption that free radicals exist. Thus,

$$C_2H_4 \rightarrow (CH_2) + (CH_2); \quad (CH_2) + C_2H_4 \rightarrow C_3H_6$$

In the absence of any definite proof, however, it is largely a matter of choice whether one prefers to explain the mechanism on the basis of free radicals or activated molecules.

"That butylene is a probable intermediate in the formation of butadiene, as has recently been stated in the literature (64), is disproved. In the cracking of propylene, there is produced about five times as much butylene as butadiene; in the cracking of ethylene, butadiene is formed in quantities about fourteen times as large as butylene. This would be inconsistent if butadiene were formed by the intermediate production of butylene. Also the method of plotting the results, as explained in the foregoing [extrapolating back to zero per cent cracking], would clearly show butadiene as a secondary product if it were formed through an intermediate as stable as butylene."

The foregoing conclusions have been questioned (28) as follows:

"The conclusion that the formation of butadiene and hydrogen is the immediate result of collision between two ethylene molecules is not justified by the data. The experimenters found it necessary to raise the temperature more than 25° to obtain the same percentage decomposition at 1.0 atmosphere as at 0.2 atmosphere. Instead of varying as the square of the pressure, which would be expected in the case of a second order reaction, the rate increased even less than the first power of the pressure. Apparently, then, the largest proportion of the substances claimed to be initial products could not readily be formed from ethylene without a bimolecular process; yet the decomposition of ethylene follows a course which is more nearly unimolecular than bimolecular. One way of correlating these observations would be to assume that the substances claimed to be initial products are rather the initial stable products which arise, in part at least, from unstable primary decomposition products of ethylene. The extrapolation method of determining primary products would not show such an effect, as may be seen when this method is applied to the decomposition of iso-butene at 700°. The curve indicated ethylene as a primary product, which is apparently im-

possible since the formation of ethylene from isobutene involves the rupture of two separate bonds. The probable explanation, suggested by Hurd (72), is that propylene, one of the primary products, decomposes to form ethylene. Acetylene, produced by dehydrogenation, would be a primary product involving the necessary first order reaction. When the concentration of ethylene is high, i.e., when the decomposition is not extensive, the probable sequel to acetylene formation would be reaction between ethylene and acetylene to form butadiene, a bimolecular process. If the first order reaction producing acetylene is more rapid than the secondary reaction in which it is consumed, it becomes understandable how a decomposition that appears to be of less than second order results in the formation of products which require a bimolecular mechanism. The assumption in this case is that acetylene is produced in considerable quantities and reacts with ethylene almost as rapidly as ethylene dehydrogenates to acetylene, although no direct data are available on this point."

The present authors adopt a non-polymerization view of the main course of ethene conversion, regarding the initial step as an endothermic formation of atomic hydrogen and vinyl radicals:

$$CH_2{=}CH_2 \rightarrow \dot{H} + CH_2{=}\dot{C}H$$

Union of vinyl radicals, which is an exothermic process, would give butadiene, presumably the *trans* form, as the product of a second step:

$$2CH_2{=}\dot{C}H \rightarrow CH_2{=}CH{-}CH{=}CH_2$$

The endothermicity of the first step is much greater than the exothermicity of the second, based on equivalent amounts of vinyl radicals, so that additional exothermic processes of local character become operative at the time vinyl radicals are formed. Such additional steps include: (a) association of atomic hydrogens to give molecules, (b) union of atomic hydrogens with stray vinyl radicals to re-form ethene molecules, (c) partial hydrogenation of ethene by atomic hydrogen, yielding ethyl radicals, (d) union of ethyls with atomic hydrogen, developing ethane, (e) coupling of ethyl radicals to give n-butane, (f) addition of ethyl and stray vinyl radicals to form butene-1, and (g) polymerization (46) of ethene, producing butene-1 and higher polymers. Steps c and d are additive, as are c plus e:

$$CH_2{=}CH_2 + \dot{H} \longrightarrow CH_3{-}\dot{C}H_2 + E_1$$

$$CH_3{-}\dot{C}H_2 + \dot{H} \longrightarrow CH_3{-}CH_3 + E_2$$

$$CH_2{=}CH_2 + 2\dot{H} \longrightarrow CH_3{-}CH_3 + E_1 + E_2$$

$$2CH_2{=}CH_2 + 2\dot{H} \longrightarrow 2CH_3{-}\dot{C}H_2 + 2E_1$$

$$2CH_3{-}\dot{C}H_2 \longrightarrow CH_3{-}CH_2{-}CH_2{-}CH_3 + E_3$$

$$\overline{2CH_2{=}CH_2 + 2\dot{H} \longrightarrow CH_3{-}CH_2{-}CH_2{-}CH_3 + 2E_1 + E_3}$$

The order of increasing exothermicity per two hydrogen atoms or one molecule of butadiene is probably $E_1 + E_2$, $2E_1 + E_3$, whereby the following over-all reaction is predictable for an ideal conversion:

$$4CH_2{=}CH_2 \rightarrow CH_3{-}CH_2{-}CH_2{-}CH_3 + CH_2{=}CH{-}CH{=}CH_2$$

Side reactions would divert much of the *n*-butane into scission products, including additional butadiene.

Favorable to the vinyl interpretation is the fact that the optimum temperature point for the non-catalytic production of butadiene from ethene is above 600°C., considerably higher than the temperature for maximum true polymerization of ethene (27). The investigated temperature range for the conversion of ethene into butadiene is 600–1100°C., but corresponding pressures are not fixed in value (33). An optimum temperature point of 750°C. is reported by one group of workers, who obtained 0.93 weight per cent of butadiene from ethene (164). Other data indicate that 650°C., at which a 4.5 weight per cent yield was obtained, is better than higher temperatures (158). High ethene conversions were obtained at 776°, 848°, and 884°C. by decreasing the contact time with each increase in temperature (144). A maximum butadiene yield of 7.3 weight per cent per pass was obtained. Large amounts of butane and butadiene result when ethene is subjected to a high-frequency discharge (4, 5). The investigators of the last reaction proposed three types of chain reactions to explain the formation of the foregoing products:

I. (1) $CH_2{=}CH_2 + e' \longrightarrow CH_2{=}\overset{|}{CH} + H + e$

(2) $CH_2{=}\overset{|}{CH} + CH_2{=}CH_2 \longrightarrow \overset{|}{CH_2}{-}CH_2{-}CH{=}CH_2$

(3) $H + CH_2{=}CH_2 \longrightarrow H_2 + CH_2{=}\overset{|}{CH}$

(4) $H_2 + \overset{|}{CH_2}{-}CH_2{-}CH{=}CH_2 \rightarrow H + CH_3{-}CH_2{-}CH{=}CH_2$

(5) $CH_3{-}CH_2{-}CH{=}CH_2 + H \longrightarrow CH_3{-}CH_2{-}CH_2{-}\overset{|}{CH_2}$

(6) $CH_3{-}CH_2{-}CH_2{-}\overset{|}{CH_2} + H_2 \rightarrow CH_3{-}CH_2{-}CH_2{-}CH_3 + H$

II. (1) $CH_2{=}CH_2 + e' \longrightarrow CH_2{=}\overset{|}{CH} + H + e$

(2) $H + CH_2{=}\overset{|}{CH} \longrightarrow CH_2{=}\overset{\|}{C} + H_2 \longrightarrow CH{\equiv}CH + H_2$

(3) $CH{\equiv}CH + H \longrightarrow H_2 + CH{\equiv}\overset{|}{C}$

(4) $CH{\equiv}\overset{|}{C} + CH{\equiv}CH \longrightarrow CH{\equiv}C{-}CH{=}\overset{|}{CH}$

(5) $CH{\equiv}C{-}CH{=}\overset{|}{CH} + H_2 \longrightarrow CH{\equiv}C{-}CH{=}CH_2 + H$

(6) $CH{\equiv}C{-}CH{=}CH_2 + H \longrightarrow CH_2{=}\overset{|}{C}{-}CH{=}CH_2$

(7) $CH_2{=}\overset{|}{C}{-}CH{=}CH_2 + H_2 \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + H$

III. (1) $CH_2{=}CH_2 + e' \longrightarrow CH_2{=}\overset{|}{C}H + H + e$

     (2) $H + CH_2{=}\overset{|}{C}H \longrightarrow CH_2{=}\overset{\|}{C} + H_2 \longrightarrow CH{\equiv}CH + H_2$

     (3) $CH_2{=}\overset{|}{C}H + CH{\equiv}CH \longrightarrow CH_2{=}CH{-}CH{=}\overset{|}{C}H$

     (4) $CH_2{=}CH{-}CH{=}\overset{|}{C}H + H_2 \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + H$

Equation 1 represents the action of an "activated electron" or "activated particle" upon ethene to form a vinyl radical. Type I chain reactions are equivalent to the process,

$$2CH_2{=}CH_2 + H_2 \rightarrow CH_3{-}CH_2{-}CH_2{-}CH_3$$

upon which is superimposed the extra step:

$$CH_2{=}CH_2 \rightarrow CH_2{=}\overset{|}{C}H + \overset{|}{H}$$

Type II chain reactions represent the over-all process,

$$CH_2{=}CH_2 + CH{\equiv}CH \rightarrow CH_2{=}CH{-}CH{=}CH_2$$

whereas those of Type III correspond to:

$$CH_2{=}CH_2 + CH_2{=}\overset{|}{C}H \rightarrow CH_2{=}CH{-}CH{=}CH_2 + \overset{|}{H}$$

All three types of chain reactions are improperly balanced for ethene *per se* processes, although they could be compounded in the following manner:

$$4CH_2{=}CH_2 \rightarrow CH_3{-}CH_2{-}CH_2{-}CH_3 + CH_2{=}CH{-}CH{=}CH_2$$

We presume that thermal conversion is too rapid for any of the three types of chain reactions to become operative and point out that an activated C—H bond explains the results of exposure to high-frequency discharges just as well as chain reactions do (154).

b. Propene

The thermal conversion of propene at 650–1400°C. is an interesting process, though difficult to explain on a mechanistic basis. Wheeler and Wood take the viewpoint that propene primarily decomposes into ethene and butene (158):

$$2C_3H_6 \rightarrow C_2H_4 + C_4H_8$$

Dehydrogenation of butene into butadiene follows. In the presence of hydrogen, some propene may decompose through the scission of the carbon chain at the C—C bond, forming radicals that hydrogenate to methane and ethene:

$$CH_3{-}CH{=}CH_2 \rightarrow \overset{|}{C}H_3 + \overset{|}{C}H{=}CH_2 \xrightarrow{H_2} CH_4 + C_2H_4$$

Ethene from propene decomposition could produce butadiene by polymerization to butene followed by dehydrogenation.

The proposed primary reaction for propene conversion is worthy of discussion. It may be regarded as a bimolecular exchange of a free methyl radical and atomic hydrogen between propene molecules (ionic formulations appear formidable):

$$CH_2{=}HC{\cdot}\overline{|{\cdot}CH_3} + \overline{|H{\cdot}|}{\cdot}CH_2{-}CH{=}CH_2 \longrightarrow$$

$$CH_2{=}HC{:}H + H_3C{:}CH_2{-}CH{=}CH_2$$
$$\text{Ethene} \qquad\qquad \text{Butene-1}$$

$$CH_2{=}HC{\cdot}\overline{|{\cdot}CH_3} + \overline{|H{\cdot}|}{\cdot}CH{=}CH{-}CH_3 \longrightarrow$$

$$CH_2{=}HC{:}H + H_3C{:}CH{=}CH{-}CH_3$$
$$\text{Ethene} \qquad\qquad \text{Butene-2}$$

Because of reëstablishment of bonds qualitatively and quantitatively, both processes would be thermoneutral in character. According to the equations, butene-1 or butene-2 would be the intermediate for butadiene formation, depending on the type of hydrogen atom scission. Schmidt's double-bond rule suggests that butene-1 is the principal intermediary product, although the required demethylation or dehydrogenation beginning with loss of a 3-position hydrogen atom is enigmatic. This alkene, however, is less rapidly converted (155) into butadiene at 1100°C. than is butene-2, which suggests that the latter isomer may be the precursor. Moreover, this view is fortified by the occurrence of an isomerization of butene-1 into butene-2 under thermal conditions (38). The investigated temperature range (650–1400°C.) for propene conversion (33) is higher than that for butene-1 isomerization (400–700°C.), so that a positive decision in favor of 1,4 dehydrogenation cannot be made at present. If 1,4 loss of hydrogen occurs, *cis*-butadiene is formed from *cis*-butene-2 and immediately leads to the ordinary *cis* and *trans* mixture:

A third bimolecular formulation is that of Frolich, Simard, and White (55) and of Schneider and Frolich (142):

$$CH_2{=}HC{\cdot}\overline{|{\cdot}CH_3} + \overline{H_3C{\cdot}|}{\cdot}CH{=}CH_2 \rightarrow H_3C{:}CH_3 + CH_2{=}HC{:}CH{=}CH_2$$
$$\text{Ethane} \qquad\qquad \text{Butadiene}$$

This process departs twice from the β-bond rule of Schmidt. Schneider and Frolich extrapolated their data back to zero per cent cracking and drew the following conclusions:

"For each 100 moles of propylene reacting, 23 or 24 moles of both butylene and ethylene are formed as initial products. Hence, it must be concluded that about 48 per cent of the propylene reacts according to the equation

$$2C_3H_6 \rightarrow C_2H_4 + C_4H_8.$$

Likewise, it seems that about 10 per cent goes to form ethane and butadiene by the reaction

$$2C_3H_6 \rightarrow C_2H_6 + C_4H_6."$$

These "initial" reactions were criticized as follows (29):

"If the above equation represents the initial steps in the decomposition, one would expect the reactions to be bimolecular. However, it was observed that 'the amount of propylene reacting is actually increased threefold' when its partial pressure was reduced from one to one-eighth atmosphere by dilution with an inert gas. This indicates that the hydrocarbons which appear on the graph as initial products were not formed as the immediate result of bimolecular collisions between propylene molecules, but rather in a series of changes in which 'free radicals or activated molecules' are the intermediates. If the initial steps in the decomposition are represented by the equations:

$$CH_3—CH{=}CH_2 \rightleftarrows CH_3 + CH{=}CH_2$$
$$\qquad\qquad\qquad\qquad\quad |\qquad\quad |$$

$$CH_3—CH{=}CH_2 \rightleftarrows CH_3CH + CH_2$$
$$\qquad\qquad\qquad\qquad\qquad \|\qquad\quad \|$$

$$CH_3—CH{=}CH_2 \rightleftarrows H + CH_2—CH{=}CH_2$$
$$\qquad\qquad\qquad\qquad\quad |\qquad |$$

there should be no decrease in the reaction rate when the partial pressure of propylene is lowered from one to one-eighth atmosphere, whereas a retardation rather than the observed increase in the reaction rate would be expected if the initial steps in the decomposition are bimolecular reactions between propylene molecules."

A fourth bimolecular formulation takes advantage of the simultaneous presence of ethene and propene from preliminary reactions (55):

$$CH_2{=}HC \cdot \overline{| \cdot H + CH_3 \cdot |} \cdot CH{=}CH_2 \longrightarrow H:CH_3 + CH_2{=}HC:CH{=}CH_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{Methane}\qquad\quad \text{Butadiene}$$

An entirely different view of propene conversion was taken in Tropsch's study (155):

"Data show that under mild conditions there is a contraction; and as the conditions become more severe, a point is reached where there is no change in volume, showing that the expansion which results from decomposition is equal to the contraction in volume from polymerization (112). If, however, the conditions are still more severe, decomposition will mask the polymerization and only the increase in volume will be observed. . . .

"The polymer obtained in the primary reaction would be unstable under the experimental conditions, partly decomposing to yield the observed gaseous products."

One may assume, therefore, that propene undergoes a dimerization into hexene-1, hexene-2, and 2,3-dimethylbutene-1,

$$CH_2=CH-H_2C \cdot \cdot H \,|\, + \,CH_2\overset{|}{-}CH-CH_3$$

$$CH_2=CH-H_2C:CH_2-HC(:H)-CH_3$$
Hexene-1

$$\overline{CH_3-CH=HC \cdot}\,|\cdot H \,+\, CH_2\overset{|}{-}CH-CH_3$$

$$CH_3-CH\!=\!\!HC:CH_2-HC(:H)-CH_3$$
Hexene-2

$$CH_2=\underset{CH_3}{\overset{|}{C}}\cdot \cdot H + \underset{CH_3}{\overset{|}{C}H\overset{|}{-}CH_2} \longrightarrow CH_2=\underset{H_3C \;\; CH_3}{\overset{|}{C}:\overset{|}{C}H-CH_2(:H)}$$

2,3-Dimethylbutene-1

and that this reaction is competitive with formation of free vinyl plus free methyl radicals:

$$CH_2=CH\cdot\cdot CH_3 \to CH_2=\overset{\cdot}{C}H + \overset{\cdot}{C}H_3$$

The transfer of a hydrogen atom can be made the last step:

$$CH_3-\overset{\cdot}{C}H-H_2\overset{\cdot}{C} + \overset{\cdot}{C}H_2-\overset{\cdot}{C}H-CH_3 \longrightarrow$$

$$CH_3-\overset{\cdot}{C}H-H_2C:CH_2-\overset{\cdot}{C}H-CH_3$$
Hexane-2,5-diyl

$$CH_3-\overset{\cdot}{C}H-H_2C:CH_2-\overset{\cdot}{C}H-CH_3 \longrightarrow CH_3-CH=HC-CH_2-CH_2-CH_3$$

Each of these six equations can be considered as representing the beginning of a process yielding butadiene. The succeeding steps will be considered next.

At 650–700°C. hexene-1 forms a small amount (106) of butadiene such as would be expected of a substance related to propene. According to Schmidt's double-bond rule, activation of hexene-1, followed by scission, should give a mixture of prop-1-en-3-yl ($CH_2=CHCH_2$) and n-propyl or, less favorably, one of hex-1-en-3-yl ($CH_2=CHCHCH_2CH_2CH_3$) plus a hydrogen atom. Butadiene is not expected. We postulate, therefore, an isomerization of hexene-1 into hexene-2 under thermal conditions in the conversion of propene. The corresponding catalytic isomerization is well established but is competitive with the formation of still other isomers (39).

Hexene-2 has not been tested for ability to form butadiene. Theoretically, it is expected to undergo initial scissions as follows:

$$CH_3—CH=CH—CH_2 \cdot \cdot CH_2—CH_3 \longrightarrow$$

$$CH_3—CH=CH—\overset{.}{C}H_2 + \overset{.}{C}H_2—CH_3$$

$$H \cdot \cdot CH_2—CH=CH—CH_2—CH_2—CH_3 \longrightarrow$$

$$\overset{.}{H} + \overset{.}{C}H_2—CH=CH—CH_2—CH_2—CH_3$$

$$H \cdot \cdot CH_2—CH \overset{..}{—} CH—CH_2 \cdot \cdot CH_2—CH_3 \longrightarrow$$

$$\overset{.}{H} + \overset{.}{C}H_2—\overset{.}{C}H—\overset{.}{C}H—\overset{.}{C}H_2 + \overset{.}{C}H_2—CH_3$$

$$CH_2=CH—CH=CH_2$$

These equations are arranged in order of increasing energy requirement, i.e., scission of one C—C bond, of one C—H bond, or of one C—C bond plus one C—H bond plus the "unsaturated half" of a C=C linkage. Further conversion of the free radical products would yield butadiene in the manner:

$$H \cdot \cdot CH_2—CH=CH—\overset{.}{C}H_2 \rightarrow \overset{.}{H} + \overset{.}{C}H_2—CH=CH—\overset{.}{C}H_2$$

$$\overset{.}{C}H_2—CH=CH—CH_2 \cdot \cdot CH_2—CH_3 \rightarrow \overset{.}{C}H_2—CH=CH—\overset{.}{C}H_2 + \overset{.}{C}H_2—CH_3$$

These equations are given in order of decreasing endothermicity. Ethyl radicals would unite with or lose hydrogen atoms, but could also form n-butane:

$$\overset{.}{C}H_2—CH_3 + \overset{.}{H} \rightarrow H:CH_2—CH_3 \text{ (ethane)}$$

$$\overset{.}{C}H_2—CH_3 \rightarrow \overset{.}{H} + CH_2 \overset{..}{—} CH_2 \text{ (ethene)}$$

$$2\overset{.}{C}H_2—CH_3 \rightarrow CH_3—CH_2:CH_2—CH_3 \text{ (butane)}$$

$$2\overset{.}{H} \rightarrow H:H$$

Therefore, the conversions of hexene-2 are expected to follow the following courses:

$$CH_3—CH=CH—CH_2—CH_2—CH_3 \rightarrow CH_2=CH—CH=CH_2 + C_2H_6$$

$$2CH_3—CH=CH—CH_2—CH_2—CH_3 \rightarrow 2CH_2=CH—CH=CH_2$$
$$+ CH_3—CH_2—CH_2—CH_3 + H_2$$

$$CH_3—CH=CH—CH_2—CH_2—CH_3 \rightarrow CH_2=CH—CH=CH_2 + C_2H_4 + H_2$$

The arrangement is in order of increasing endothermicity, i.e., decreasing probability of occurrence unless the thermal input is excessive.

Over-all equations are now available for the conversions of propene passing through a hexene-1 or hexene-2 stage:

$$2CH_2\!\!=\!\!CH\!\!-\!\!CH_3 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + C_2H_6$$

$$4CH_2\!\!=\!\!CH\!\!-\!\!CH_3 \rightarrow 2CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + C_4H_{10} + H_2$$

$$2CH_2\!\!=\!\!CH\!\!-\!\!CH_3 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + C_2H_4 + H_2$$

Hexene-3, attributable to isomerization of hexene-1 or hexene-2, should yield butadiene by demethylation:

$$H_3C\cdot\cdot CH_2\!\!-\!\!CH\!\!\doteq\!\!CH\!\!-\!\!H_2C\cdot\cdot CH_3 \cdot \quad 2CH_3 + CH_2\!\!-\!\!CH\!\!-\!\!CH\!\!-\!\!CH_2$$

$$\Updownarrow$$

$$CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2$$

$$2CH_3 \quad H_3C\!:\!CH_3 \text{ (ethane)}$$

The over-all equation is:

$$2CH_2\!\!=\!\!CH\!\!-\!\!CH_3 \cdot \quad CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + C_2H_6$$

Hexene-3 conversion is expected to be slightly exothermic. Confirmatory experimental work is unavailable.

2,3-Dimethylbutene-1 and 2,3-dimethylbutene-2 have not been considered in the literature from the conversion viewpoint. The first alkene would require demethylation, probably once by elimination of methane and once by hydrogenolysis or by formation of ethene:

$$H_2C\!\!=\!\!C\!\!-\!\!CH\!\!-\!\!CH_2 \qquad 2H\!:\!CH_3 + H_2C\!\!=\!\!C\!\!-\!\!CH\!\!-\!\!CH_2$$

$$\begin{matrix} & H & & & H \\ H_3 & H_3 & & Methane & Butadiene \end{matrix}$$

$$H\cdot\cdot H$$

$$H_2C\!\!=\!\!C\!\!-\!\!CH\!\!-\!\!CH_2$$

$$H\cdot \quad \boxed{\begin{matrix} \dot{C} & \dot{H} \\ H_3 & \end{matrix}}$$
$$H_2$$

$$\boxed{\begin{matrix} H_2 & H_3 \\ C & H \end{matrix}}$$
$$H\cdot\cdot C$$

$$2H\!:\!CH_3 + H_2C\!:\!:CH_2 + 2H_2C\!\!=\!\!C\!\!-\!\!CH\!\!-\!\!CH_2$$

$$\ddot{H}$$

$$H_2C\!\!=\!\!C\!\!-\!\!CH\!\!-\!\!CH_2 \qquad Methane \qquad Ethene \qquad Butadiene$$

An objection may be raised against the hydrogenolysis of a methyl group without saturation of a double bond in juxtaposition. Both hydrogen reactions would be exothermic, the latter predominantly so. Therefore, ethene formation through the union of methylene groups as high-temperature scission products is also postulated. Removal of the 3-methyl group would be in conformity with

Schmidt's double-bond rule. That of the 2-methyl group would be contrariwise, although probable at high temperatures. A concomitant removal of both methyl groups, forming butadiene-1,2 and ethane, would still require a final isomerization:

$$H_2C\!=\!C\!-\!CH\!-\!CH_3 \qquad \cdot\ H_2C\!=\!C\!\!-\!\!CH\!-\!CH_3 \ +\ H_3C\!:\!CH_3$$

$$|H_3\dot{C}\quad \dot{C}H_3| \qquad\qquad \text{Butadiene-1,2}\qquad \text{Ethane}$$

$$CH_2\!=\!CH\!\!-\!\!CH\!=\!CH_2$$

The proximity of methyl groups in the 2- and 3-positions would favor the conversion, and prior dissociation of the 3-methyl radical in conformity with the β-bond rule might make it possible.

2,3-Dimethylbutene-2 should be convertible into butadiene after isomerization to the alkene-1 or by any of the following processes:

$$CH_3\!-\!C\!=\!C\!-\!CH_3 \qquad CH_3\!-\!C\!\!-\!\!C\!-\!CH_3 \ +\ H_3C\!:\!CH_3$$

$$|H_3C\quad CH_3| \qquad\qquad \text{Butyne-2}\qquad \text{Ethane}$$

$$CH_2\!=\!CH\!\!-\!\!CH\!=\!CH_2$$

$$CH_3\!-\!C\!=\!C\!-\!CH_2 \qquad\quad 2H\!:\!CH_3 \ +\ CH_3\!-\!C\!=\!C\!-\!CH_2$$

$$\begin{array}{cc} C & C\ H| \\ H_3 & H_3 \end{array} \qquad\qquad \text{Methane} \qquad \text{But-2-ene-1,2-diyl}$$

$$H.\ .H \qquad CH_2\!-\!CH\!-\!CH\!-\!CH_2 \ \longleftarrow\ CH_2\!-\!C\!=\!C\!-\!CH_2$$

$$CH_2\!=\!CH\!\!-\!\!CH\!=\!CH_2 \qquad\qquad H\ H$$

$$\text{But-2-ene-1,4-diyl}$$

$$CH_3\!-\!C\!=\!C\!-\!CH_2$$

$$H.\!\cdot\!\begin{array}{cc} \dot{C} & C\ H \\ H_2 & H_3 \end{array}$$

$$H.\!\cdot\!\begin{array}{cc} H_2 & H_3 \\ \dot{C} & C\ H \end{array} \qquad 2H\!:\!CH_3 \ +\ H_2C\!::\!CH_2 \ +\ 2CH_3\!-\!C\!=\!C\!-\!CH_2$$

$$CH_3\!-\!\dot{C}\!=\!C\!-\!C| \qquad\qquad H$$

$$\text{Methane}\qquad\text{Ethene}\qquad \text{But-2-ene-1,2-diyl}$$

$$2CH_2\!-\!CH\!-\!CH\!-\!CH_2 \qquad 2CH_2\!-\!C\!=\!C\!-\!CH_2$$

$$CH_2\!=\!CH\!\!-\!\!CH\!=\!CH_2 \qquad\qquad H\ H$$

$$\text{But-2-ene-1,4-diyl}$$

A hydrogen atmosphere is indicated for the second process, rather than dependence upon the operation of local dehydrogenations.

We now return to the scission of propene into free vinyl and free methyl radicals, a change which was assumed to be competitive with the polymerization

of propene into hexenes. Vinyl radicals would yield butadiene through electronic coupling:

$$CH_2=H\overset{.}{C} + \overset{.}{C}H=CH_2 \rightarrow CH_2=HC:CH=CH_2$$

An inspection of the over-all equation,

$$2CH_2=CH-CH_3 \rightarrow CH_2=CH-CH=CH_2 + CH_3-CH_3$$

indicates that equal numbers of C—C bonds are broken and re-formed. Successful conversion of propene requires a preferential activation and scission of the methyl-to-vinyl linkage. The new bond formation that follows should be facilitated by instantaneous removal of the excitation energy and through the introduction of endothermic processes immediately after the scission. In support of the free-radical formulation there can be cited the results of cracking propene at 600°C. in the presence of hydrogen (75). These showed greatly increased percentages of methane and ethene over yields from propene alone.

c. Butenes

Butene-1 apparently requires only dehydrogenation to form butadiene:

$$CH_2=CH-CH_2-CH_3 \longrightarrow CH_2=CH-\overset{.}{C}H-CH_3 + \overset{.}{H}$$

$$CH_2=CH-\overset{.}{C}H-CH_3 \longrightarrow CH_2=CH-\overset{.}{C}H-\overset{.}{C}H_2 + \overset{.}{H}$$

$$2\overset{.}{H} \longrightarrow H:H$$

$$CH_2=CH-\overset{.}{C}H-\overset{.}{C}H_2 \rightleftharpoons CH_2=CH-CH=CH_2$$

$$\overline{CH_2=CH-CH_2-CH_3 \longrightarrow CH_2=CH-CH=CH_2 + H_2}$$

A conversion through loss of atomic hydrogens is illustrated; the "stabilization" of but-1-ene-3,4-diyl ($CH_2=CH\overset{.}{C}H\overset{.}{C}H_2$) into the covalent alkadiene cannot be regarded as an additional step. Schmidt's double-bond rule suggests that but-1-en-3-yl ($CH_2=CH\overset{.}{C}HCH_3$) rather than but-1-en-4-yl ($CH_2=CHCH_2\overset{.}{C}H_2$) is the intermediate yielding the butenediyl. The entire dehydrogenation can be conducted thermally (33) or catalytically (6, 36).

Butene-2 requires 1,4 dehydrogenation and central bond activation for conversion into butadiene:

$$CH_3-CH=CH-CH_3 \longrightarrow \overset{.}{C}H_2-\overset{.}{C}H-\overset{.}{C}H-\overset{.}{C}H_2 + H:H$$

$$\overset{.}{C}H_2-\overset{.}{C}H-\overset{.}{C}H-\overset{.}{C}H_2 \rightleftharpoons CH_2=CH-CH=CH_2$$

$$\overline{CH_3-CH=CH-CH_3 \longrightarrow CH_2=CH-CH=CH_2 + H_2}$$

In the discussion on propene conversion, a formulation for 1,4 dehydrogenation of *cis*-butene-2 to give *cis*-butadiene and eventually the *trans*-alkadiene was presented. A direct conversion of *trans*-butene-2 into *trans*-butadiene appears less probable:

$$
\begin{array}{c}
\text{H} \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C} \\
\diagdown \quad \diagup\diagup \\
\text{C} \qquad \text{CH}_2 \\
\text{H} \qquad \text{H}
\end{array}
\longrightarrow
\begin{array}{c}
\text{H} \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C}\cdot \\
\diagdown \quad \diagup \\
\text{C}\cdot \qquad \text{CH}_2 \\
\text{H}
\end{array}
+ \ \dot{\text{H}}
$$

$$
\begin{array}{c}
\text{H} \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C}\cdot \\
\diagdown \quad \diagup \\
\text{C}\cdot \qquad \text{CH}_2 \\
\text{H}
\end{array}
\longrightarrow
\begin{array}{c}
\text{H} \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C} \\
\diagdown \quad \diagup\diagup \\
\text{C}\cdot \qquad \text{CH}_2 \\
\text{H}
\end{array}
$$

$$
\begin{array}{c}
\text{H} \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C} \\
\diagdown \quad \diagup\diagup \\
\text{C}\cdot \qquad \text{CH}_2 \\
\text{H}
\end{array}
\longrightarrow
\begin{array}{c}
\qquad \qquad \text{H} \\
\text{H}_2\dot{\text{C}} \qquad \text{C} \\
\diagdown \quad \diagup\diagup \\
\text{C}\cdot \qquad \text{CH}_2 \\
\text{H}
\end{array}
+ \ \dot{\text{H}}
$$

$$2\dot{\text{H}} \longrightarrow \text{H:H}$$

$$
\begin{array}{c}
\qquad \qquad \text{H} \\
\text{H}_2\dot{\text{C}} \qquad \text{C} \\
\diagdown \quad \diagup\diagup \\
\text{C}\cdot \qquad \text{CH}_2 \\
\text{H}
\end{array}
\rightleftharpoons
\begin{array}{c}
\qquad \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C} \\
\diagdown\diagdown \quad \diagup\diagup \\
\text{C} \qquad \text{CH}_2 \\
\text{H}
\end{array}
$$

$$
\begin{array}{c}
\text{H} \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C} \\
\diagdown \quad \diagup\diagup\diagdown \\
\text{C} \qquad \text{CH}_2 \\
\text{H} \qquad \text{H}
\end{array}
\longrightarrow
\begin{array}{c}
\qquad \qquad \text{H} \\
\text{H}_2\text{C} \qquad \text{C} \\
\diagdown\diagdown \quad \diagup\diagup \\
\text{C} \qquad \text{CH}_2 \\
\text{H}
\end{array}
+ \ \text{H}_2
$$

The conversion of butene-2 may be conducted thermally (33) or catalytically (36). A catalyst facilitates the steps indicated for thermal conversion by aiding or performing the following operations: (a) activation of the double bond, (b) removal of atomic hydrogen from butene-2 or but-1-en-3-yl ($CH_2\!\!=\!\!CHCHCH_3$), (c) formation of but-1-en-3-yl from butane-1,2,3-triyl ($CH_2CHCHCH_3$), (d) transfer of the energy released upon but-1-en-3-yl formation to the C—H bond in the 4-position, and (e) union of atomic hydrogens to form molecules.

In practice, it is not necessary to utilize an individual butene. Much data are available concerning the catalytic dehydrogenation of mixtures of butene-1 and butene-2 over chromia or other catalysts (36, 57, 109). Limited data are concerned with the corresponding thermal treatment (33). Even 2-methylpropene has been converted into butadiene and other products (155). A study of the equilibrium dehydrogenation of butene-1 and butene-2 into butadiene at 480–534°C. over a chromia catalyst indicates that the reaction is about 29 kcal. endothermic (19).

d. Pentenes

Pentene-1 and pentene-2 are almost equally convertible into butadiene at 600°C. or 650°C. in the presence of steam (106). A similar conversion of pen-

tene-2 occurred at 600°C. in the absence of steam (112). The mechanism of the last reaction was formulated as follows:

$$CH_3CH{=}CHCH_2CH_3 \rightarrow CH_3CH{=}CHCH_2 + CH_3$$

$$CH_3CH{=}CHCH_2 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H$$

Formation of methane and butene-2 was ascribed to hydrogenation of primary radicals by hydrogen released in but-2-en-1-yl conversion or carbon deposition:

$$CH_3CH{=}CHCH_2 + CH_3 + 2H \rightarrow CH_3CH{=}CHCH_3 + CH_4$$

The conversion of pentene-1 into butadiene may proceed in two ways: A preliminary isomerization into pentene-2 suggests itself from the work of Hurd (70, 74). An alternative mechanism, available for high thermal input rates, consists of demethanation by (*a*) activation of the double bond, (*b*) loss of a hydrogen atom in the β-position to the activated double bond, (*c*) formation of pent-2-en-1-yl (CH₂CH=CHCH₂CH₃) from pentane-1,2,3-triyl (CH₂CHCHCH₂CH₃), (*d*) full activation of the C—C bond holding the terminal methyl group, and (*e*) union of atomic hydrogen and the free methyl radical to form methane:

$$\overset{H}{\underset{|}{CH_2}}{-}CH{-}CH{-}CH_2{-}CH_3 \rightarrow CH_2{-}CH{-}CH{-}CH_2{-}CH_3 + H$$

$$CH_2{-}CH{-}CH{-}CH_2{-}CH_3 \rightarrow CH_2{-}CH{=}CH{-}CH_2{-}CH_3$$

$$CH_2{-}CH{=}CH{-}CH_2{\cdot\cdot}CH_3 \rightarrow CH_2{-}CH{=}CH{-}CH_2 + CH_3$$

$$CH_2{-}CH{=}CH{-}CH_2 \rightleftarrows CH_2{-}CH{-}CH{-}CH_2 \rightleftarrows CH_2{=}CH{-}CH{=}CH_2$$

$$H + CH_3 \rightarrow H{:}CH_3$$

Demethylation of pentane-1,2,3-triyl should be possible also, but this would probably require a higher temperature than 600°C.

To explain the frequent and then (1913) often unexpected formation of butadiene in the thermal treatment of straight-chain or cyclic hydrocarbons, Ostromyslenskiĭ formulated the following rule (122):

"Straight chain hydrocarbons containing one double bond or saturated cyclic hydrocarbons, regardless of their structure or molecular weight, eliminate under the action of high temperature a saturated hydrocarbon and not hydrogen. In this reaction, side-chain radicals are split off, including all carbon atoms with the exception of four, which include the two carbon atoms connected by the double bond, thus forming butadiene."[1]

Details of the foregoing conversions were purposely omitted in order to avoid complicating the discussion. The rôles of isomerization and of cyclobutene formation, however, were considered:

$$\begin{array}{ccc} H_2C{-}CH_2R & H_2C{-}CHR \\ | & | \quad | \\ HC{=}CH_2 & H_2C{-}CH_2 \end{array} \xrightarrow{\ -HR\ } \begin{array}{c} H_2C{-}CH \\ | \quad \| \\ H_2C{-}CH \end{array} \rightarrow \begin{array}{c} H_2C{=}CH \\ | \\ H_2C{=}CH \end{array}$$

According to Ostromyslenskiǐ, alkenes and cyclanes containing five or more carbon atoms per molecule must persistently retain four such atoms in thermal decomposition. In some cases, isomerization of the primary product was postulated, such that a linear chain of four carbon atoms results. Also, in hydrocarbons above butene and cyclobutane in size, demethanation and de-ethanation must occur more easily than elimination of molecular hydrogen. The rule does not mention hydrocarbons with less than four carbon atoms per molecule; it was presumed that these members easily condense at high temperatures into convertible hydrocarbons. As examples of the decomposition of alkenes into butadiene, the conversions of 3-methylbutene-1 and 2-methyl-butene-2 were cited (122):

$$CH_2{=}CH{-}CH(CH_3)_2 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + CH_4$$

$$(CH_3)_2C{=}CH{-}CH_3 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + CH_4$$

A later publication (124) omits the foregoing rule and replaces it by the statement, "elimination of RH (R being an alkyl group) from straight chain hydrocarbons containing a single double bond," a process that was expressed by the equation:

$$RC_4H_7 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + RH$$

where C_4H_7 is presumably any linear butenyl group (i.e., but-1-en-1-, 2-, 3-, or 4-yl and but-2-en-1- or 2-yl), and that was substantiated by a reaction of new type, namely, a depolymerization of alkenes accompanied by dehydrogenation or dealkanation:

$$C_8H_{16} \text{ ("dibutene")} \rightarrow 2CH_2{=}CH{-}CH{=}CH_2 + 2H_2$$

$$C_{10}H_{20} \text{ ("diamylene")} \rightarrow 2CH_2{=}CH{-}CH{=}CH_2 + 2CH_4$$

The structures of the two alkenes were not considered. Formation of 2-methyl-butadiene-1,3 (i.e., isoprene) in the pyrolysis of its natural aliphatic dimer, myrcene, was admitted but not regarded as atypical. However, the views of Perkin and Weizmann (130), Staudinger (47), and others (119) regarding enhanced dehydrogenation of branched pentenes into 2-methylbutadiene-1,3 were claimed to be erroneous. Schotz disagrees with this claim (143):

"Suppose Ostromyslenskiǐ's experiments are correct, the apparent contradiction can be explained quite simply: We have seen in discussing the preparation of isoprene from petro-

leum according to French Patent Specification 435,312 that it is an established fact that trimethylethylene is produced from two other amylenes under certain conditions, and no doubt may also be transformed into isomeric compounds. Owing to the unstable nature of these unsaturated bodies the results depend on so many factors that it is unwise to doubt observations made by chemists of high standing."

Ostromyslenskiĭ's rule (122) can be regarded as a foreshadowing of our C_4 directive fragmentation theory, which is more applicable to linear than to cyclic molecules. Ring strain, despite its neglect by Ostromyslenskiĭ, is an important factor governing the conversion of cyclic hydrocarbons.

e. Hexadecene

Hexadecene is the largest alkene yet investigated from the standpoint of butadiene formation. One group of investigators obtained a 1 per cent yield at 550°C. and interpreted its data by a series of equations (56):

(1) $CH_3 \vert CH_2—(CH_2)_{12}—CH=CH_2 \rightarrow$

$$CH_2=CH—(CH_2)_{11}—CH=CH_2 + CH_4$$

(2) $CH_3—CH_2 \vert CH_2—CH_2—(CH_2)_{10}—CH=CH_2 \rightarrow$

$$CH_2=CH—(CH_2)_{10}—CH=CH_2 + CH_3—CH_3$$

(3) $CH_3—CH_2—CH_2 \vert CH_2—CH_2—(CH_2)_9—CH=CH_2 \rightarrow$

$$CH_2=CH—(CH_2)_9—CH=CH_2 + CH_3—CH_2—CH_3, \text{ etc.}$$

(4) $CH_2=CH—(CH_2)_{10}—CH_2 \vert CH=CH_2 \rightarrow$

$$CH_2=CH—(CH_2)_9—CH=CH_2 + CH_2=CH_2$$

(5) $CH_2=CH—(CH_2)_9—CH_2 \vert CH_2—CH=CH_2 \rightarrow$

$$CH_2=CH—(CH_2)_8—CH=CH_2 + CH_3—CH=CH_2$$

(6) $CH_2=CH—(CH_2)_8—CH_2 \vert CH_2—CH_2—CH=CH_2 \rightarrow$

$$CH_2=CH—(CH_2)_7—CH=CH_2 + CH_3—CH_2—CH=CH_2, \text{ etc.}$$

(7) $CH_2=CH—CH_2—CH_2 \vert CH=CH_2 \rightarrow$

$$CH_2=CH—CH=CH_2 + CH_2=CH_2, \text{ etc.}$$

(8) $CH_2=CH—(CH_2)_8—CH_2 \vert CH_2—CH_2—CH=CH_2 \rightarrow$

$$CH_2=CH—(CH_2)_7—CH=CH_2 + CH_2=CH—CH=CH_2$$

Equations 1, 2, and 3 represent supposed changes in the primary reaction as the temperature or thermal input increases. The resulting alkadienes were assumed to undergo secondary reactions according to equations 4, 5, and 6. Tertiary reactions, 7 and 8, were proposed as the final phases of thermal degradation.

The foregoing equations admit of three distinct ways of butadiene formation:

(9) $CH_3—(CH_2)_{13}—CH=CH_2 \rightarrow CH_2=CH—(CH_2)_2—CH=CH_2$
$+ CH_3—(CH_2)_8—CH_3$

(7) $CH_2=CH—(CH_2)_2—CH=CH_2 \rightarrow CH_2=CH—CH=CH_2 + CH_2=CH_2$

(1) $CH_3—CH_2—(CH_2)_{12}—CH=CH_2 \rightarrow CH_2=CH—(CH_2)_{11}—CH=CH_2$
$+ CH_4$

(10) $CH_2=CH—(CH_2)_{11}—CH=CH_2 \rightarrow CH_2=CH—(CH_2)_2—CH=CH_2$
$+ CH_3—(CH_2)_6—CH=CH_2$

(7) $CH_2=CH—(CH_2)_2—CH=CH_2 \rightarrow CH_2=CH—CH=CH_2 + CH_2=CH_2$

(1) $CH_3—CH_2—(CH_2)_{12}—CH=CH_2 \rightarrow CH_2=CH—(CH_2)_{11}—CH=CH_2$
$+ CH_4$

(11) $CH_2=CH—(CH_2)_{11}—CH=CH_2 \rightarrow CH_2=CH—(CH_2)_8—CH_3$
$+ CH_2=CH—CH=CH_2$

Equation 11 replaces equation 8, which has a hydrogen deficiency as originally written. Otherwise, hydrogen gas would have to be included as a product and its formation specifically provided for in the investigators' interpretation.

We now proceed to discuss the three implied mechanisms. In all cases, the first reaction is given as a dealkanation. The final reaction is represented as the debutadienation of a higher alkadiene.

Demethanation of hexadecene-1 (equation 1) is probably an unimportant "primary" reaction. Its complexity, moreover, is indicated by the required operation on linkages, namely, breakage of a C—C bond, then of a C—H bond, followed by closure of atomic hydrogen upon the free methyl radical to form methane and by formation of a double bond. In the cracking of hexadecene under pressure, the carbon chain seems to break near the double bond (67). If the hexadecene molecule introduced originally has and thereafter retains its double bond in the terminal position, demethanation has the advantage of forming two symmetrical products. On the other hand, demethanation is contrary to several principles already considered. Thus, C_2 directive fragmentation would lead to formation of ethene and its polymers. A C_4 directive fragmentation would easily account for the butadiene production. Its operation would furnish a supply of atomic hydrogen that could cause extensive hydrogenolysis into methane and higher alkanes. Demethanation "at low temperatures" is contrary to Schmidt's double-bond rule, whereby the following products should develop from the several straight-chain hexadecenes that constitute or probably arise from "hexadecene:"

INITIAL HEXADECENE	"PRIMARY" PRODUCTS	
	Unstable	Stabilized
Hexadecene-1.	Prop-1-en-3-yl Tridecyl-1	Propene or propadiene Tridecane or tridecene-1
Hexadecene-2.	Atomic hydrogen But-2-ene-1,4-diyl Dodecyl-1	Hydrogen Butadiene Dodecane or dodecene-1
Hexadecene-3..	Methyl But-2-ene-1,4-diyl Hendecyl-1	Methane or ethane or ethene Butadiene Hendecane or dodecane or hendecene-1
Hexadecene-4.	Ethyl But-2-ene-1,4-diyl Decyl-1	Ethane or butane or ethene Butadiene Decane or dodecane or decene-1
Hexadecene-5.	n-Propyl But-2-ene-1,4-diyl Nonyl-1	Propane or hexane or propene Butadiene Nonane or dodecane or nonene-1
Hexadecene-6.	n-Butyl But-2-ene-1,4-diyl Octyl-1	Butane or octane or butene-1 Butadiene Octane or dodecane or octene-1
Hexadecene-7.	Pentyl-1 But-2-ene-1,4-diyl Heptyl-1	Pentane or decane or pentene-1 Butadiene Heptane or dodecane or heptene-1
Hexadecene-8..	Hexyl-1 But-2-ene-1,4-diyl	Hexane or dodecane or hexene-1 Butadiene

According to the double-bond rule, the reported pyrolysis products should have had 24.1 weight per cent of butadiene except from unisomerized hexadecene-1. One may assume, therefore, that the formation (observed) of cyclic hydrocarbons was responsible for low yields of this alkadiene at 500–600°C.

Dedecanation of hexadecene-1 to yield hexadiene-1,5 as per equation 9 can be considered as the start of an interesting speculation. The subsequent equation 7 represents the operation of both C_2H_4 and C_4H_6 directive fragmentations. Actually, cyclization products mainly replaced butadiene. Catalytic conversion of hexadecene over neutral or alkaline catalysts devoid of cyclization tendency (40) suggests itself. Inhibitors may be useful.

Denonenation of pentadecadiene-1,14 in the manner of equation 10 was not considered to be an important source of a lower alkadiene. Equation 7, however, was set up as an example of a reaction terminating a degradation series. Equations 1, 10, and 7 obviously represent a minor source of the total butadiene actually produced or producible. More probable ways of formation of this alkadiene are conceivable.

The debutadienation of pentadecadiene-1,14 was neglected by its proposers.

It is best represented according to equation 11 and is an example of C_4H_6 directive fragmentation at the end of a long molecule. Because it does not follow the double-bond rule, we assume that it is operative mainly at high temperatures.

Regarding the possibility of a 48.2, 72.3, or 96.4 weight per cent yield of butadiene from straight-chain hexadecenes, by the formation of two, three, or four molecules of alkadiene per one of alkene, it can be stated that two paths of investigation are available to the researcher. One consists of depolymerization of straight-chain hexadecenes into straight-chain octenes, or even into butenes-1 and -2, prior to dehydrogenation. The other path aims at direct scission of hexadecene into C_4 fragments by selective activation of the molecule. That the latter is not unattainable can be seen from the few methods of increasing molecular energy investigated to date and from the many methods available for delineation of modes of molecular distortion or vibrations.

3. Alkadienes

2-Methylbutadiene-1,3 undergoes a slight "demethylenation" to butadiene when passed at 600–820°C. through tubes packed with coke (148). The conversion was believed to be dependent upon a cracking of by-products, including 2-methylbutene-2, hydroaromatic hydrocarbons, and aromatics. For example, 1,4 hydrogenation would give 2-methylbutene-2, which upon demethanation would form butadiene:

$$CH_2=C(CH_3)-CH=CH_2 + 2\overset{\cdot}{H} \rightarrow CH_3-C(CH_3)=CH-CH_3$$

$$CH_3-C(CH_3)=CH-CH_3 \rightarrow CH_2=CH-CH=CH_2 + CH_4$$

Polymerization of 2-methylbutadiene-1,3 would give limonene-like dimers, and subsequent side-chain scissions could lead to cyclohexene formation, explaining any conversion of "hydroaromatic hydrocarbons:"

"Dipentene"

Isolimonene $CH_2=CH-CH=CH_2 + C_2H_4$

An isomerization of dipentene is depicted, so that Schmidt's double-bond rule is satisfied; carbonization would release the four hydrogen atoms required for hydrogenolysis to methane and propene. Cyclohexene due to the hydrogenation of benzene also might be available; it was demonstrated that the cracking of 2-methylbutene-2 gives a tar containing benzene, naphthalene, and anthracene. Cyclohexene is readily converted into a mixture of butadiene and ethene. The present authors favor a direct demethylenation of 2-methylbutadiene-1,3, as follows:

$$CH_2{=}C{-}CH{=}CH_2$$

$$\longrightarrow \quad 2CH_2{=}C{-}CH{=}CH_2 \ + \ H_2C{::}CH_2$$

Ethene

2,3-Dimethylbutadiene-1,3 forms a small amount of butadiene at 700–800°C. (148). In lieu of a conversion proceeding via the tars formed, the following demethylenations can be considered:

(A) $CH_2{=}C{-}C{=}CH_2 \longrightarrow CH_2{=}C{-}C{=}CH_2 \ + \ H_2C{::}CH_2$

(B) $CH_2{=}C{-}C{=}CH_2$

$$\longrightarrow \quad 2CH_2{=}C{-}C{=}CH_2 \ + \ H_2C{::}CH_2$$

$$2CH_2{=}C{-}C{=}CH_2$$

$$CH_2{=}C{-}CH{=}CH_2$$

$$\longrightarrow \quad 2CH_2{=}C{-}CH{=}CH_2 \ + \ H_2C{::}CH_2$$

(C) $CH_2=C-C=CH_2$

$$2CH_2=C-C=CH_2 + 2H_2C::CH_2$$

The processes A, B, and C are equally endothermic, though quite dissimilar from the viewpoint of probability of reaction. Processes A and C would require the presence of *cis* molecules, whereas process B would operate on either *cis* or *trans* forms. Process A represents an almost unknown type of reaction. In process B, competitive reactions might greatly reduce the yield of butadiene. The simultaneous tetrademethylenation between two molecules, process C, seems practically excluded on the basis of a preferential didemethylenation between two molecules, yielding 2-methylbutadiene-1,3.

4. Alkynes

Ethyne produces an interesting mixture of hydrogen, methane, ethane, ethene, propene, propadiene, butadiene, ethyne, propyne, benzene, toluene, and naphthalene when passed at 420–430°C. over a zinc chloride on pumice catalyst (100). Exposure of ethyne, with or without ethene, to a high-frequency corona discharge results in a slight formation of butadiene (4). The investigators of the last reaction have proposed the following mechanisms in explanation (*e′* is an activating particle):

In the absence of ethene:

$$CH{\equiv}CH + e' \longrightarrow CH{\equiv}C + H + e$$

$$CH{\equiv}CH + H \longrightarrow CH{\equiv}C + H_2$$

$$CH{\equiv}C + HC{\equiv}CH \longrightarrow CH{\equiv}C-CH=CH$$

$$CH{\equiv}C-CH=CH + H_2 \longrightarrow CH{\equiv}C-CH=CH_2 + H$$

$$CH{\equiv}C-CH=CH_2 + H \longrightarrow CH_2=C-CH=CH_2$$

$$CH_2=C-CH=CH_2 + H_2 \longrightarrow CH_2=CH-CH=CH_2 + H$$

In the presence of ethene:

$$CH{\equiv}CH + e' \longrightarrow \overset{|}{CH}{\equiv}C + H + e$$

$$CH_2{=}CH_2 + H \longrightarrow \overset{|}{CH_2}{=}CH + H_2$$

$$\overset{|}{CH_2}{=}CH + CH{\equiv}CH \longrightarrow CH_2{=}CH{-}\overset{|}{CH}{=}CH$$

$$CH_2{=}CH{-}\overset{|}{CH}{=}CH + H_2 \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + H$$

In the first scheme, butenyne assumes the rôle of an intermediate, while hydrogen is obtained through the cracking of ethyne. The second group of equations was considered to be complementary to the three types of chain reactions, already discussed, pertaining to the conversion of ethene by exposure to the high-frequency discharge (5).

A union of ethene-1,2-diyls ($\overset{\cdot}{C}H{=}\overset{\cdot}{C}H$) with available atomic hydrogens, followed by association of the ensuing free vinyl radicals, is favored by the present authors in lieu of the first chain-reaction scheme:

$$CH{\equiv}CH \rightleftarrows \overset{\cdot}{C}H{=}\overset{\cdot}{C}H$$

$$\overset{\cdot}{C}H{=}\overset{\cdot}{C}H + \overset{\cdot}{H} \rightarrow CH_2{=}\overset{\cdot}{C}H$$

$$2CH_2{=}\overset{\cdot}{C}H \rightarrow CH_2{=}CH{:}CH{=}CH_2$$

Less favored than the present set of reactions, though more acceptable than the chain-reaction mechanism, is the association of ethene-1,2-diyls ($\overset{\cdot}{C}H{=}\overset{\cdot}{C}H$) to form buta-1,3-diene-1,4-diyl ($\overset{\cdot}{C}H{=}CHCH{=}\overset{\cdot}{C}H$), followed by union of the latter with available atomic hydrogens:

$$CH{\equiv}CH \rightleftarrows \overset{\cdot}{C}H{=}\overset{\cdot}{C}H$$

$$2\overset{\cdot}{C}H{=}\overset{\cdot}{C}H \rightarrow \overset{\cdot}{C}H{=}CH{:}CH{=}\overset{\cdot}{C}H$$

$$\overset{\cdot}{C}H{=}CH{:}CH{=}\overset{\cdot}{C}H + 2\overset{\cdot}{H} \rightarrow CH_2{=}CH{:}CH{=}CH_2$$

This mechanism finds support in the formation of thiophene and some butadiene from ethyne at 300–310°C. in the presence of iron pyrites (151).

For the ethene and ethyne juncture, a formation and union of free ethanediyl and ethenediyl radicals is suggested:

$$CH_2{=}CH_2 \rightleftarrows \overset{\cdot}{C}H_2{-}\overset{\cdot}{C}H_2$$

$$CH{\equiv}CH \rightleftarrows \overset{\cdot}{C}H{=}\overset{\cdot}{C}H$$

$$\overset{\cdot}{C}H_2{-}\overset{\cdot}{C}H_2 + \overset{\cdot}{C}H{=}\overset{\cdot}{C}H \rightarrow \overset{\cdot}{C}H_2{-}CH_2{:}CH{=}\overset{\cdot}{C}H$$

The resulting but-1-ene-1,4-diyl upon activation of its double bond, because of the exothermic character of the coupling of C_2 diyls, would form butane-1,1,2,4-tetrayl:

$$\overset{\cdot}{C}H{=}CH{-}CH_2{-}\overset{\cdot}{C}H_2 \rightarrow \overset{\cdot}{C}H{-}\overset{\cdot}{C}H{-}CH_2{-}\overset{\cdot}{C}H_2$$

Isomerization would then give but-1-ene-3,4-diyl and covalent butadiene:

$$\overset{\cdot}{C}H{-}\overset{\cdot}{C}H{-}CH_2{-}\overset{\cdot}{C}H_2 \longrightarrow \overset{\cdot}{C}H{=}CH{-}\overset{\cdot}{C}H{-}\overset{\cdot}{C}H_2$$
$$\overset{\vdots}{H}$$

$$\overset{\cdot}{C}H{=}CH{-}\overset{\cdot}{C}H{-}\overset{\cdot}{C}H_2 \longrightarrow CH_2{=}CH{-}\overset{\cdot}{C}H{-}\overset{\cdot}{C}H_2 \rightleftarrows CH_2{=}CH{-}CH{=}CH_2$$
$$\overset{\vdots}{H}$$

Ethene and ethyne mixtures are convertible into butadiene also by direct thermal (37, 160) or catalytic (37, 90, 92) methods. However, the De Boistesselin and Dubosc process for the production of artificial rubber first converts the mixture into butyne-1 over animal charcoal at 150°C. and then forms butadiene by isomerizing the product at 300°C. over pumice (22). A catalytic type of interaction between ethyne and ethanol at temperatures above 350°C. is claimed in an old patent application (80). Catalytic dehydration of the ethanol would presumably give ethene, which could then unite with ethyne. The presence of steam would not be inimical unless other components of the catalyst favor hydration of ethyne (9, 110).

Butyne-1 and butyne-2 are readily isomerized to butadiene over catalysts such as magnesium oxide at 460°C. *in vacuo* or in the presence of diluent gases (35). The isomerizations are favored by the exothermic nature of the change of one C—C and one C≡C into two C=C bonds.

5. Alkenyne

Butenyne can be hydrogenated to butadiene by contact with (a) hydrogen gas and an iron, cobalt, nickel, palladium, or platinum catalyst, (b) aqueous solution of chromous sulfate containing free sulfuric acid, or (c) zinc dust and solutions of alkaline substances (35). Electrolytic hydrogenation over a platinized electrode is highly selective, not producing butenes simultaneously, contrary to hydrogenations (a) catalyzed by Ginzberg's or Paal's palladium, Willstätter's platinum black, Zelinskii and Komarewsky's nickel on alumina catalyst, or (b) effected by contact with water and the copper–zinc couple (95). In all these cases, the *desired* hydrogenation probably proceeds by addition of neutral, atomic hydrogen to buta-1,3-diene-1,2-diyl ($\overset{\cdot}{C}H{=}\overset{\cdot}{C}{-}CH{=}CH_2$):

$$CH{\equiv}C{-}CH{=}CH_2 \rightarrow \overset{\cdot}{C}H{=}\overset{\cdot}{C}{-}CH{=}CH_2$$

$$\overset{\cdot}{C}H{=}\overset{\cdot}{C}{-}CH{=}CH_2 + 2H \rightarrow CH_2{=}CH{-}CH{=}CH_2$$

The function of Group VIII elements in atomic hydrogenation seems to be "galvanic in nature," with an electron flowing from molecular hydrogen to the metal and from the charged metal to the proton just generated. Close approaches to this mechanism exist in the literature (10, 16, 83). The surfaces of zinc metal and of the copper–zinc couple, like those of the enumerated Group VIII metals, probably temporarily bind and thus conserve atomic hydrogens, but generation of the latter is their principal function.

6. Alkadiyne

Butadiyne has been converted into butadiene by contact with (a) hydrogen gas in the presence of reduced nickel, platinum, palladium, or copper (11), (b) acidified solution of chromous chloride or sulfate (82), or (c) zinc dust and sodium hydroxide solution (132). As in the hydrogenation of butenyne, these conversions are probably all dependent upon a supply of neutral hydrogen atoms. Hydrogenation should proceed, therefore, by 1,2 and 1,4 addition, forming butenyne and the unknown butatriene, respectively. The latter would probably immediately isomerize to butenyne or hydrogenate to butadiene. Butenyne from both sources would then undergo its normal hydrogenation to the conjugated alkadiene.

B. CYCLIC SERIES

1. Cyclanes

Methylenecyclopropane is converted into butadiene by isomerization at 350°C. over alumina (104). It involves scission of a linkage in the α-position to the double bond, apparently contrary to Schmidt's rule. In formulating the reaction mechanism, a priori discussions are obligatory because the ordinary molecular model sets do not contain tetravalent spheres or "carbon atoms" machined for strained rings. We take the primary step to be an activation of the molecule, particularly that of the double bond:

The two π electrons are considered to remain in their activated or open state throughout the conversion into butadiene. Following opening of the double bond, a loosening of a C—H linkage at either "ring CH$_2$" group is postulated, being incited by proximity of the free valency on the side chain as the latter rotates about the C—C bond:

Next, there is projected a scission of the loosened hydrogen atom as it follows the field of the rotating side chain and enters that of the other two carbon atoms, forming an "activated complex:"

The concluding step, whereby *trans*-butadiene is formed, is passage of the complex over a low potential barrier in the direction of this product:

The action of high temperature on methylcyclobutane (120) and cyclopentane (50, 120) results in butadiene formation. Ostromyslenskiĭ explained the cyclopentane conversion as an isomerization to methylcyclobutane, followed by demethanation to cyclobutene and then by β-bond scission (120):

$$\text{cyclopentane} \longrightarrow \overset{CH_3}{\text{cyclobutane}} \xrightarrow{(-CH_4)} \text{cyclobutene} \longrightarrow CH_2{=}CH{-}CH{=}CH_2$$

Unfortunately, both cyclopentane and cyclobutene remain unisomerized to date (41). Thermal treatments of methylcyclopentane (50· 133) and "dimethylcyclopentane" (50) also yield butadiene.

Lurie (101) considered that thermal decompositions of cyclopentane and methylcyclopentane afford butadiene indirectly through ethene, propene, and, in the case of methylcyclopentane, also *via* butene-2:

$$
\begin{array}{l}
CH_2{-}CH_2 + CH_2{-}CH_2{-}CH_2 \qquad C_2H_4 + CH_2{=}CH{-}CH_3 \\
\quad | \qquad\quad | \qquad\quad | \qquad\qquad | \\[4pt]
\text{cyclopentane} + H_2 \qquad\qquad + 2H_2
\end{array}
$$

$$
\begin{array}{l}
CH_2{-}CH_2{-}CH_2 + CH_2{-}CH{-}CH_3 \cdot \quad 2CH_2{=}CH{-}CH_3 \\
\quad | \qquad\qquad | \qquad\quad | \qquad\quad | \\[6pt]
CH_2{-}CH_2 + CH_2{-}CH_2{-}CH{-}CH_3 \rightarrow \\
\quad | \qquad\quad | \qquad\quad | \qquad\qquad | \\
\qquad\qquad\qquad\qquad C_2H_4 + CH_3{-}CH{=}CH{-}CH_3 \\[6pt]
CH_2{-}CH_2 + CH_2{-}CH(CH_3){-}CH_2 \rightarrow \\
\quad | \qquad\quad | \qquad\quad | \qquad\qquad | \\
\qquad\qquad\qquad\qquad C_2H_4 + CH_2{=}C(CH_3)_2
\end{array}
$$

These equations are essentially those of Kazanskiĭ and Platé (87, 88), with the exception of that for butene-2 formation, which was added by Lurie. Kazanskiĭ and Platé failed to find butadiene definitely among the products of the thermal treatment of cyclopentane at 600–800°C. and of methylcyclopentane at 600° or 650°C. Frey's data (53) substantiate the equations just given for the decomposition of cyclopentane.

Rice and Rice postulated an initial formation of pentane-1,5-diyl (i.e., pentamethylene) from cyclopentane (134). Scission of this diyl was considered to give ethene and propene by way of the corresponding diyls:

$$CH_2\!-\!CH_2\!-\!CH_2\!-\!CH_2\!-\!CH_2 \longrightarrow CH_2\!-\!CH_2 +$$
$$CH_2\!-\!CH_2\!-\!CH_2 \longrightarrow CH_2\!=\!CH_2 + CH_2\!=\!CH\!-\!CH_3$$

They also reflected upon the formation of pent-2-ene-1,5-diyl from cyclopentene of dehydrogenation, indicating that its scission would yield ethene and propadiene *via* ethane-1,2-diyl and prop-1-ene-1,3-diyl:

$$\bigcirc \xrightarrow{(-H_2)} \diagdown \!\!\!\!\!\bigcirc\!\!\!\! \diagup \longrightarrow CH_2\!-\!CH\!=\!CH\!-\!CH_2\!-\!CH_2$$
$$\downarrow$$
$$CH_2\!=\!C\!=\!CH_2 + CH_2\!=\!CH_2 \longleftarrow CH_2\!-\!CH\!=\!CH + CH_2\!-\!CH_2$$

On the contrary, our opinion is that the aforesaid products are those expected from an isomeric diyl, pent-1-ene-1,5-diyl ($\dot{C}H\!=\!CHCH_2CH_2\dot{C}H_2$), and that pent-2-ene-1,5-diyl should form some butadiene and methylene by a C_4H_6 directive fragmentation:

$$CH_2\!-\!CH\!=\!CH\!-\!CH_2\!-\!CH_2 \rightarrow CH_2\!-\!CH\!=\!CH\!-\!CH_2 + CH_2$$

Cyclohexane is convertible into butadiene by thermal treatment at 600–870°C. with 5–36 weight per cent yields per pass (33, 152), or at 539°C. with 12 min. contact time (93), or by catalysis over calcium oxide at 680°C. (81). High pressures are inimical toward the thermal or catalytic conversion (62). The primary reaction in thermal conversion is commonly regarded as dehydrogenation to cyclohexene (84, 88). This cyclene is generally considered to be the common precursor of butadiene and benzene. Pease and Morton first observed a well-marked induction period in the thermal conversion, which delay they ascribed to a slow isomerization, a chain reaction, or a close balance between dissociation and polymerization (129). Data on the established isomerization of cyclohexane into methylcyclopentane indicate that the reaction is endothermic, yielding also dissociation and condensation products (42). This accounts for the observed stasis in pressure measurements.

Cyclohexane and methylcyclopentane exist in a state of pseudoequilibrium under conditions yielding butadiene; hence both isomers may participate in its formation. Lurie has discussed the mechanism (*cf. infra*) of butadiene formation from methylcyclopentane (101). It involves scission into ethane-1,2-diyl $(\dot{C}H_2\dot{C}H_2)$ and butane-1,3-diyl $(\dot{C}H_2CH_2\dot{C}HCH_3)$, conversion of these into ethene and butene-2, respectively, and dehydrogenation of the latter. Of course, under the requisite high-temperature conditions, the excited rather than ground states of methylcyclopentane, ethene, and butene-2 would prevail.

According to Rice and Rice, two primary decomposition mechanisms are possible for cyclohexane (135). Ethene and butene-2, also cyclohexene and hydrogen, are the primary reaction products. Each of these hydrocarbons produces a certain amount of butadiene, but cyclohexene does so in direct competition with aromatization into benzene:

$$CH_2-CH_2-CH_2-CH_2-CH_2-CH_2 \rightarrow C_2H_4 + CH_3-CH=CH-CH_3$$

$$CH_2-CH=CH-CH_2-CH_2-CH_2 \rightarrow C_2H_4 + CH_2=CH-CH=CH_2$$

Schmidt considers the mechanism of butadiene formation from cyclohexane to be the following (140):

"There is no doubt that by cracking cycloparaffins, such as cyclohexane, the greater part of the molecule is first dehydrogenated to tetrahydrobenzene and then split into two fragments, butadiene and ethylene, as I have shown (139). Therefore the series of reactions with primary dehydrogenation and scission on the weak positions 3 and 3' is experimentally well founded.

"... As we have seen, in most of the molecules two C—H bonds are broken and tetra-hydrobenzene is formed, which then gives butadiene and ethylene; but a small part of cyclohexane first gives α-hexylene and a carbon bond is broken according to the scheme:

I   II   III   IV

Schmidt's hypothesis that butadiene comes exclusively from cyclohexene (i.e., tetrahydrobenzene) appears too restricted. One may presume that sufficient activation of any two adjacent (*ortho* position) hydrogen atoms of cyclohexane would furnish an activated state of the molecule having weakened β-bonds. Upon scission of the mutual β-bond, giving hexane-1,6-diyl ($\dot{C}H_2CH_2CH_2CH_2$-$CH_2\dot{C}H_2$), there would appear hexene-1, hexene-2, and hexene-3 as interconvertible isomers. The last two isomers presumably would obey the double-bond rule, yielding ethane and butadiene:

$$CH_3—CH=CH—CH_2—CH_2—CH_3 \longrightarrow \left[CH_3—CH=CH—\underset{|}{C}H_2 \; + \right.$$

$$\left. \underset{|}{C}H_2—CH_3 \right] \longrightarrow C_2H_6 \; + \; CH_2=CH—CH=CH_2$$

$$CH_3—CH_2—CH=CH—CH_2—CH_3 \longrightarrow \left[\underset{|}{C}H_3 \; + \right.$$

$$\left. \underset{|}{C}H_2—CH=CH—\underset{|}{C}H_2 \; + \; CH_3 \right] \longrightarrow C_2H_6 \; + \; CH_2=CH—CH=CH_2$$

At high temperatures, cyclohexane probably undergoes a C_2H_4 directive fragmentation ("depolymerization" to ethene and butene, or ethene exclusively), beginning with the formation of hexane-1,6-diyl. Butadiene would then result from the dehydrogenation of the butenes and the association of vinyl radicals traceable to ethene. Butenes (-1 and -2) for dehydrogenation could also result from the polymerization of ethene.

Methylcyclohexane and "dimethylcyclohexanes" produce butadiene upon contact with hot surfaces, such as electrically heated aluminum silicates (66). Passage of methylcyclohexane or ethylcyclohexane through a quartz tube at 700–

750°C. in the presence of steam forms butadiene in considerable amounts (165). Two over-all equations can be given for the conversion of methylcyclohexane:

$$C_7H_{14} \rightarrow C_4H_6 + CH_4 + C_2H_4$$

$$2C_7H_{14} \rightarrow 2C_4H_6 + 2C_2H_6 + C_2H_4$$

The first equation corresponds to a demethanation into cyclohexene, which is a less endothermic reaction than dehydrogenation to a methylcyclohexene. Demethanation probably involves two steps of decomposition:

$$C_7H_{14} \rightarrow \overset{\cdot}{C}_6H_{11} + \overset{\cdot}{C}H_3$$

$$\overset{\cdot}{C}_6H_{11} \rightarrow C_6H_{10} + \overset{\cdot}{H}$$

$$\overset{\cdot}{C}H_3 + \overset{\cdot}{H} \rightarrow CH_4$$

The second over-all equation corresponds to the main products when steam is used to facilitate formation of butadiene. Evidently, the last condition favors a greater mingling of free radicals, with the result that atomic hydrogen combines with ethane-1,2-diyl rather than methyl:

$$2C_7H_{14} \longrightarrow 2C_6H_{10} + 2\overset{\cdot}{C}H_3 + 2\overset{\cdot}{H}$$

$$2\overset{\cdot}{C}H_3 \longrightarrow H_3C:CH_3$$

$$2C_6H_{10} \longrightarrow 2C_4H_6 + 2\overset{\cdot}{C}H_2 - \overset{\cdot}{C}H_2$$

$$\overset{\cdot}{C}H_2 - \overset{\cdot}{C}H_2 + 2\overset{\cdot}{H} \longrightarrow CH_3 - CH_3$$

$$\overset{\cdot}{C}H_2 - \overset{\cdot}{C}H_2 \rightleftarrows CH_2 = CH_2$$

$$2C_7H_{14} \longrightarrow 2C_4H_6 + 2C_2H_6 + C_2H_4$$

The absolute pressure in the work with steam was probably 0.1 atmosphere, which would aid in the distribution of free radicals.

Ethylcyclohexane probably forms butadiene according to the two equations:

$$C_8H_{16} \rightarrow CH_2 = CH - CH = CH_2 + CH_2 = CH - CH_2 - CH_3 + H_2$$

$$C_8H_{16} \rightarrow 2CH_2 = CH - CH = CH_2 + 2H_2$$

In the first equation, the assumption is made that ring dehydrogenation precedes ring scission, as is probable in the conversion of cyclohexane. 1-Ethylcyclohexene-3 of dehydrogenation would undergo a C_4H_6 directive fragmentation, forming butadiene and butene-1:

cis-Butadiene-1,3　　　　Butene-1

If the butene-1 undergoes 3,4 dehydrogenation, then the first over-all equation gives way to the second, as also occurs when 1-vinylcyclohexene-3 forms from 1-ethylcyclohexene-3:

cis　　　　$trans$

In the preceding equation, a formation of cis-butadiene from ring atoms in 2-, 3-, 4-, and 5-positions and of the $trans$ form from all atoms in 1- and 6-positions of the ring is intended. As these products cool, more $trans$ form develops by isomerization. A $trans$ configuration for the vinyl group with respect to ring atoms 1 and 6 is specified because of steric interference (repulsion) between the ring-closest gem hydrogen atom of the vinyl group and one or the other of the hydrogen atoms in ring position 6, depending on which of the two possible

orientations prevails for the 1,6 ring atoms with respect to the common plane of the remaining ring atoms.

The viewpoint that the second over-all equation is possible follows in part from the facts that 1-vinylcyclohexene-3 is the cyclic dimer (94, 97, 98, 99) of butadiene and that it readily depolymerizes (166) at 500–600°C. The endothermic heat of decomposition of 1-vinylcyclohexene-3 is 23 kcal. per converted gram-mole (48). Dehydrogenation of ethylcyclohexane or ethylcyclohexene is also endothermic. Since these energy requirements are additive, it is evident that the first over-all reaction is most probable:

$$C_8H_{16} \rightarrow C_4H_6 + C_4H_8 + H_2$$

Allylcyclohexane upon thermal treatment yields a trace of butadiene among a great preponderance of decomposition products (73). It does not appear to be convertible in a direct manner.

2. Cyclenes

1-Methylcyclopropene-1 forms butadiene when isomerized at 325°C. over alumina (105). In formulating the reaction mechanism, a decision must be made between scission of the C=C bond to give a C—C linkage and that of a C—H bond in the methyl group as the primary act following an activation of the molecule by the catalyst. The energy expenditure is least in the first process, which leads to the equation:

With release of the two electrons, a simultaneous enlargement or slight stabilization of the ring system must occur, owing to the greater length of C—C as compared to C=C bonds (128). Following these two changes, the loosening of a methyl-group hydrogen atom would occur, as expected from the double-bond rule of Schmidt:

Activation of the double bond does not detract from the applicability of the rule, since β-bond scission is also concerned with bond angles and distances. An allylic type of hydrogen migration, equivalent to forming an active form of methylenecyclopropane, is not postulated because of the detour from the desirable open-bond state of the two carbon atoms destined to form the middle portion of the butadiene molecule.

The fourth step is taken to be a further loosening of the foregoing C—H bond,

by formation of a one-electron bond, presumably with the aid of weak attractive forces between the ring CH_2 group and the lone electron:

$$HC\text{---}C\text{---}CH_2 \quad \longrightarrow \quad HC\text{---}C\text{---}CH_2$$

The fifth or final step, which directly forms *trans*-butadiene, is the "reaction" between three atoms in the "transition state:"

Alumina could facilitate scission of the cyclopropane ring by the formation of a one-electron bond at the ring carbon atom opposite the three-atom complex.

Cyclobutene, an isomer of butadiene, has apparently never been studied from the standpoint of isomerization (43). Reactions (20, 21, 121, 124, 126, 159) in which it is expected as the principal product usually yield the alkadiene, so that thermal and catalytic treatments are expected to give a direct conversion in good yield when polymerization or other side reactions are avoided.

Cyclopentene has been pyrolyzed at 850°C. and 10 mm. mercury absolute pressure, apparently without formation of butadiene or other C_4 products (133). Doubt can be cast upon the reported analyses, because C_2 and C_3 unsaturated aliphatic products were present in considerable quantities. The present writers, however, agree with the explanation given for side courses of the reaction: namely, the formation of pent-2-ene-1,5-diyl instead of cyclopentadiene:

$$H_2C\text{---}CH \quad \longrightarrow \quad CH_2\text{---}CH\text{=}CH\text{---}CH_2\text{---}CH_2$$

The viewpoint of the investigators was that of the "principle of least motion," postulating minimum motion of the atoms in passing from the starting to the final configurations of nuclei, and also least change of electronic configurations in the reacting system (137). Our viewpoint requires a second application of Schmidt's double-bond rule. Some but-2-ene-1,4-diyl ($CH_2CH\text{=}CCH_2$) plus methylene should develop by scission of the C—C bond in the 4,5-position. Such butenediyl radicals would immediately form covalent butadiene. Under favorable reaction conditions, therefore, the "conversion" of cyclopentene is expected to take the following course:

$$
\begin{array}{ccc}
\underset{|}{\overset{\cdot}{H_2C}}\text{——}CH & \overset{\cdot}{H_2C}\text{——}CH & \overset{\cdot}{HC}\text{——}CH \\
H_2C \quad \overset{\parallel}{CH} \longrightarrow & \overset{\parallel}{H_2C}\text{——}\overset{\cdot\cdot}{C} \to & H \\
\underset{|}{\diagdown C \diagup} & \overset{|}{H} & \overset{\parallel}{HC}\text{——}CH \quad + \quad CH_2 \\
\overset{\cdot}{H} & \cdot CH_2 & \overset{\cdot}{} \qquad 1/2\ CH_2::CH_2
\end{array}
$$

An elimination of methylene would be expected on account of proximity of the hydrogens in the 3- and 5-positions of pent-2-ene-1,5-diyl. The repulsive force set up would be aided by any interaction of 5-position lone electrons with approaching pentenediyls. Scission of methylene followed by coupling to form ethene is indicated on thermodynamic grounds also, i.e., the over-all process would be almost thermoneutral. The ethene so produced would be another, though herein minor, source of butadiene.

The conversion of cyclohexene into ethene plus butadiene has been studied extensively. Thermal treatment affords nearly 50 weight per cent of the alkadiene (34, 89). Low-pressure conditions should favor the reaction by preventing secondary changes and by overcoming an incidental formation of benzene (93, 136). Catalytic processes are available also. Calcium oxide (77), a mixture (78) of magnesium oxide with less than 5 per cent of calcium oxide, and magnesium oxide alone (81) are recommended for use as catalysts at 625°, 650°, and 680°C., respectively. According to Mailhe, the action of silica gel at 550–750°C. on cyclohexene gives a mixture of alkanes, alkenes, and aromatics (102, 103). Formation of pentadiene-1,3 was claimed for the 600° and 650°C. tests, but this may have been confused with that of butadiene because of the proximity in the melting points of 1,2,3,4-tetrabromobutane (m.p. 118°C.) and 1,2,3,4-tetrabromopentane (m.p. 114°C.). Again, the presence of tetrabromobutane may have been masked by a preponderance of the tetrabromopentane, assuming that alkylation conditions converted considerable butadiene into pentadiene-1,3, just as they alkylated the by-product benzene into toluene and m-xylene.

Rice and coworkers (136) assume that the primary step consists of a C—C bond rupture in the β-position to the double bond, in a manner analogous to the scission of alkenes (26, 70, 139, 140, 141), forming a resonating radical that decomposes immediately into ethene and butadiene.

Hurd has suggested that thermal reactions of cyclic hydrocarbons are probably analogous to the chain reactions applied to alkanes, i.e., the chains are perpetuated by some radical (71). Cyclohexene, upon loss of a 3-position hydrogen atom followed by γ-bond scission between carbon atoms 4 and 5, would accordingly form hexa-1,3-dien-6-yl (CH₂=CHCH=CHCH₂CH₂—).

Further conversion, not following Schmidt's double-bond rule, would give a hydrogen atom plus hexatriene-1,3,5 or else ethene and buta-1,3-dien-1-yl:

$$\text{(cyclohexene)} \xrightarrow{-H} \text{(cyclohexenyl-H)}$$

$$
\begin{array}{c}
\text{H}_2\text{C} \\
| \\
\text{H}_2\text{C}
\end{array}
\begin{array}{c}
\text{H} \\
\text{C} \\
\diagdown \\
\\
\diagup \\
\text{C} \\
\text{H}_2
\end{array}
\begin{array}{c}
\text{CH} \\
\\
\text{CH}
\end{array}
\left\langle
\begin{array}{l}
\text{H} + \text{CH}_2\!\!=\!\!\text{CH}\!\!-\!\!\text{CH}\!\!=\!\!\text{CH}\!\!-\!\!\text{CH}\!\!=\!\!\text{CH}_2 \\
| \\[6pt]
\text{CH}_2\!\!=\!\!\text{CH}_2 + \text{CH}\!\!=\!\!\text{CH}\!\!-\!\!\text{CH}\!\!=\!\!\text{CH}_2 \\
\qquad\qquad\quad |
\end{array}
\right.
$$

Union of butadienyl and a hydrogen atom would yield butadiene. Scission of cyclohex-1-en-3-yl between carbon atoms 5 and 6, in the conventional β-bond manner, was considered to give hexa-1,4-dien-6-yl ($\text{CH}_2\!\!=\!\!\text{CHCH}_2\text{CH}\!\!=\!\!\text{CH}\text{-CH}_2\!\!-$) and eventually polymers, rather than the now expected butadiene:

$$\text{(cyclohexenyl-H)} \longrightarrow \text{(diene)} \longrightarrow \text{polymers}$$

The present writers suggest that cyclohexene probably forms some ethene and *cis*-butadiene in one step by a mechanical twisting-off of ethane-1,2-diyl (construct molecular model!) and redistribution of the four electrons in 3,4 and 5,6 bond positions. The initial, intermediary, and final electronic configurations corresponding to this suggestion are:

$$\text{(initial)} \longrightarrow \text{(intermediary)} \longrightarrow \text{(final)}$$

1-Methylcyclohexene-1 yields much ethene and 2-methylbutadiene-1,3 but less than 1 per cent of butadiene when heated at 650–690°C. under partial vacuum conditions (165). This fact fortifies the view that Schmidt's double-bond rule is well operative in the cyclohexene series. The small formation of butadiene can be ascribed to the decomposition of its 2-methyl derivative or to the condensation of ethene under dehydrogenation conditions.

1-Methylcyclohexene-3, as expected, yields much propene plus butadiene when passed through a quartz tube at 690°C. in the presence of steam and under partial vacuum conditions (165):

The conversion of 1-vinylcyclohexene-3 into butadiene was regarded by Ostromyslenskiĭ as a true depolymerization, corresponding to that of cyclic terpenes (124, 125):

$$2CH_2=CH-CH=CH_2$$

This conception of the over-all reaction prevails to date. A C_4H_6 directive fragmentation explaining the conversion in one step has already been given (see ethylcyclohexane). An alternate explanation having two steps is ring scission between carbon atoms 1 and 2, enhanced because of the critical location of the C—C link being ruptured, i.e., in the β-position to both double bonds. The resultant free diradical, octa-1,6-diene-3,8-diyl, would undergo a conversion into two molecules of butadiene:

CH=CH₂

$$\longrightarrow CH_2=CH-CH-CH_2 \vert CH_2-CH=CH-CH_2 \longrightarrow$$
$$2CH_2=CH-CH=CH_2$$

Splitting occurs only at the 4,5 position in the diyl because its 3-position electron has already satisfied the requirement for β-bond scission with respect to the 1,2 double bond. A butadiene yield of 60 weight per cent is obtainable at 500–600°C. (166).

3. Bicyclane

Decahydronaphthalene, i.e., decalin, decomposes at 700–800°C. in the presence of steam to form about 4 weight per cent of butadiene, besides ethene, hydrogen, and other gases (165). The conversion is probably due to several reactions, including condensation of ethene or ethane, through dehydrogenation; ethenylation of ethene by ethyne; dehydrogenation of butane and butenes; chain scission

in pentane, hexane, hexenes, and butenylbenzene; and decyclization of cyclo-hexene, benzene, naphthalene, and tetrahydronaphthalene. These hydrocarbons are among those known to be formed in the thermal treatment of decahydro-naphthalene (30). From the viewpoint of Schmidt's double-bond rule, the decyclizations of 1,4,4a,5,8,8a-hexahydronaphthalene and 1,2,3,4,4a,5,8,8a-octahydronaphthalene, i.e., β-octalin, which are possible intermediates, should each give two molecules of butadiene by redistribution of electrons in the 1,8a; 4,4a; 4a,5; 8,8a and 1,2; 3,4; 4a,5; 8,8a bond positions, respectively:

Hexahydronaphthalene

Octahydronaphthalene

2 Butadiene + Ethyne

Butadiene + Cyclohexene

Butadiene + Ethene

In the case of the conversion of 1,4,4a,5,8,8a-hexahydronaphthalene, a mechanical twisting-off of ethane-1,1,2,2-tetrayl ($\cdot$CH—CH$\cdot$) is suggested by inspection of molecular models. The corresponding torsional removal of cyclohexane-1,2-diyl from 1,2,3,4,4a,5,8,8a-octahydronaphthalene would be competitive with decyclizations to the same cyclanediyl caused by repulsions between hydrogen atoms in the 1-, 2-, 3-, 4-, 4a-, and 8a-positions and those in the 5- and 8-positions, according to the following schedule (repulsions are indicated by colon marks):

<div align="center">POSITIONS OF OPPOSING HYDROGEN ATOMS</div>

1	1:8; 4:5. Reverse side shows same numbering.
2	1,1:8,8; 4,4:5,5. Reverse side shows same numbering.
3	1:8; 2:5; 4:5. Reverse side shows 1:8; 3:8; 4:5.
4	1,1:8,8; 4:5; 4a:8. Reverse side shows 1:8; 4,4:5,5; 8a:5.
5	1:5; 1:8; 4:5; 4a:8. Reverse side shows 1:8; 4:5; 4:8; 8a:5.
	1:8; 2:5; 3:5; 4a:8. Reverse side shows 2:8; 3:8; 4:5; 8a:5.
	1:8; 2:7; 3:6; 4:5. Reverse side shows same numbering.
	1:8; 2:8; 3:5; 4:5. Reverse side shows same numbering.
9	1:8; 3:8; 4:5; 8a:5. Reverse side shows 1:8; 2:5; 4:5; 4a:8.
10	1:8,8; 4,4:5,5; 4a:8; 8a:5. Reverse side shows 1,1:8,8; 4:5,5; 4a:8; 8a:5.
11	1,1:8,8; 4,4:5,5; 4a:8; 8a:5. Reverse side shows same numbering.
12	1:5; 1:8; 2:5; 4:5,5; 4a:8. Reverse side shows 1:8,8; 3:8; 4:5; 4:8; 8a:5.
13	1:5; 1:8; 3:5; 4:5; 4a:8. Reverse side shows 1:8; 2:8; 4:5; 4:8; 8a:5.
14	1:5; 1:8; 3:5,5; 4:5; 4a:8. Reverse side shows 1:8; 2:8,8; 4:5; 4:8; 8a:5.
15	1:8,8; 2:8; 4,4:5,5; 4a:8; 8a:5. Reverse side shows 1,1:8,8; 3:5; 4:5,5; 4a:8; 8a:5.

4. Mononuclear aromatic

The formation of butadiene from benzene at high temperatures was studied by Maksimov in Ostromyslenskiĭ's laboratory (117, 124). Dehydrogenation into diphenyl was considered to be the first phase of the reaction. The resultant hydrogen was believed to reduce some benzene into cyclohexane or even hexane. These products, in turn, would give butadiene plus ethene, but the over-all yield was negligible. The equation given was (124):

$$7C_6H_6 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + C_2H_4 + H_2 + 3C_6H_5\!\!-\!\!C_6H_5 \quad (A)$$

It should have been written as follows:

$$5C_6H_6 \rightarrow CH_2\!\!=\!\!CH\!\!-\!\!CH\!\!=\!\!CH_2 + C_2H_4 + 2C_6H_5\!\!-\!\!C_6H_5 \quad (B)$$

Disproportionation of benzene into diphenyl and cyclohexene was cursorily considered (121). It has the advantage of less hydrogen transfer and consequently greater probability of occurrence:

$$5C_6H_6 \rightarrow C_6H_{10} \text{ (cyclohexene)} + 2C_6H_5\!\!-\!\!C_6H_5 \quad (C)$$

$$7C_6H_6 \rightarrow C_6H_{12} \text{ (cyclohexane)} + 3C_6H_5\!\!-\!\!C_6H_5 \quad (D)$$

$$9C_6H_6 \rightarrow C_6H_{14} \text{ (hexane)} + 4C_6H_5\!\!-\!\!C_6H_5 . \quad (E)$$

Because of the regeneration of hydrogen from cyclohexane and hexane in their further transformation into butadiene, equation B still describes the over-all course of conversions proceeding through any of the paths C, D, or E.

Another explanation of benzene conversion is given by the C_4H_6 directive fragmentation theory and, having a constitutional basis, promises greatly increased yields of butadiene as knowledge of decyclization of benzene increases. An interesting elucidation of benzene, hydroxybenzene, and 1,2-dihydroxy-benzene conversions (32, 36) centers on the hypothetical elimination of unstable C_2 fragments:

$$C_6H_6 \longrightarrow \overset{.}{C}H_2\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H_2 + \cdot\overset{.}{C}\text{---}\overset{.}{C}\cdot$$

$$\text{(i.e., } CH_2\text{=}CH\text{---}CH\text{=}CH_2 + C\equiv C \text{ [or carbon lattice])}$$

$$C_6H_5OH \longrightarrow \overset{.}{C}H_2\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H_2 + \cdot\overset{.}{C}\cdot\cdot\overset{.}{C}\text{:}\overset{.}{O} \longrightarrow$$

$$\overset{.}{C}H_2\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H_2 + \cdot\overset{.}{C}\cdot + \text{:}\overset{.}{C}\text{::}O$$

$$\text{(i.e., } CH_2\text{=}CH\text{---}CH\text{=}CH_2 + \frac{1}{2} C\equiv C \text{ [or carbon lattice]} + CO)$$

$$C_6H_4(OH)_2 \longrightarrow \overset{.}{C}H_2\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H_2 + \overset{.}{O}\text{:}\overset{.}{C}\cdot\cdot\overset{.}{C}\text{:}\overset{.}{O} \longrightarrow$$

$$\overset{.}{C}H_2\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H\text{---}\overset{.}{C}H_2 + 2\text{:}\overset{.}{C}\text{::}O$$

$$\text{(i.e., } CH_2\text{=}CH\text{---}CH\text{=}CH_2 + 2CO)$$

III. Conclusions

According to theoretical formulations presented here by the authors and supported by many reported processes, butadiene can be prepared from all ordinary hydrocarbons. Certain members, such as *n*-butane, ethene, butene-1 or -2, butenyne, butyne-1 or -2, butadiyne, cyclohexane, cyclohexene, and 1-vinyl-cyclohexene-3, are highly convertible into butadiene. The clue to this behavior is their electronic and molecular structures, which approach those of butadiene. This statement applies also to the activated or momentarily reacting molecules. A deficiency of hydrogen or tendency thereto must be counteracted, as in the case of butenyne or butadiyne. If hydrogen must be removed, as with *n*-butane and the butenes, catalytic dehydrogenation gives superior results compared with thermal treatment. Although it would be desirable to dehydrogenate cyclo-hexane into cyclohexene prior to final conversion, its catalytic dehydrogenation would yield benzene. Considerable research remains to be carried out on the juncture of ethene with itself or with ethyne to produce butadiene.

Two types of molecular scission, designated as C_2 and C_4 directive fragmentations, probably exist and favor the production of butadiene from individual hydrocarbons. These scissions provide C_2 and C_4 fragments that retain their own hydrogen atoms and conceivably can become stabilized through the formation of butadiene. Schmidt's double-bond rule applies to these fragmentations,

but its scope must be extended to permit scission of a C—H bond in the β-position to a double bond.

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KINETICS AND MECHANISM OF THE BECKMANN REARRANGEMENT

BRYNMOR JONES

University of Sheffield, Sheffield, England

Progress in the field of reaction mechanism is slow and uncertain. Rarely have the mechanisms of chemical reactions been elucidated at their first investigation, and, looked at in retrospect, many of the early attempts to unravel their complexities reflect the gradual development of chemical thought and the increasing precision of physicochemical conceptions. The Beckmann rearrangement is here no exception. First observed in 1886, it was represented by Beckmann (1, 2) as a direct interchange of the hydroxyl group of the oxime and one of the hydrocarbon groups, followed by the spontaneous migration of the hydrogen to give the true amide.

$$R \diagdown C{=}NOH \longrightarrow R \diagdown C{=}NR \longrightarrow RCONHR$$
$$R \diagup \qquad\qquad HO \diagup$$

Because the rearrangement could be readily effected by a wide variety of reagents, Beckmann considered it was highly unlikely that any single intermediate compound or any single type of intermediate compound was involved, and regarded the function of the reagent as simply that of a catalyst.

Attempts to formulate a detailed mechanism soon led to controversy. Theories based on the formation of intermediate compounds put forward independently by Hantzsch (11), Wallach (28), and others had but little success, for almost invariably the compounds formulated as intermediates were found by later workers to be incapable of undergoing rearrangement (*cf*. Montagne (22) and Stieglitz and Peterson (27)). Theories based on the formation of free radicals were no more successful. For example, although recent research has emphasized the close similarity and intramolecular character of several classes of carbon–nitrogen rearrangements, such as the Beckmann rearrangement, the Hofmann degradation of amides, and the Curtius and Lossen rearrangements, Stieglitz's early attempt to coördinate them by a single mechanism achieved such coördination only by overemphasizing formal similarities at the expense of real differences (*cf*. Watson (29)).

It is not necessary here to review in detail the early theories of the mechanism of the Beckmann change. A full account of them, and of Meisenheimer's elucidation of the migration as one involving *trans* groups, have been given by Blatt[1] (3). In recent years support for Meisenheimer's view has been given by Mills (21), who has shown that a *trans* migration is probable on stereo-

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[1] A complete bibliography of the early work on the Beckmann change is given by Blatt.

chemical grounds. The simultaneous wandering of the hydroxyl and hydrocarbon groups, and the greater ease with which this can occur in *trans* rather than in *cis* migration, is shown by the model in figure 1, which is due to Mills (21).

The present article reviews the advances made in the field of the kinetics and mechanism of the rearrangement, chiefly as a result of the researches of Kuhara and Chapman. These researches have greatly enlarged our knowledge of the factors which influence the change and have contributed much towards a final solution of the problem.

The most important of the earlier investigations of the mechanism of the rearrangement are those of Kuhara (14). Carrying out an extensive investi-

FIG. 1

gation of the effect of acid chlorides, he concluded that it is the esters (acyl derivatives) of the oximes and not the oximes themselves which undergo rearrangement—a view which had been adumbrated by Sluiter (25) for the rearrangement of acetophenone oxime in concentrated sulfuric acid. Kuhara (15) found that certain esters, such as the benzenesulfonyl ester of benzophenone oxime, rearranged spontaneously, while others, such as the acetate, required the presence of hydrogen chloride to bring about rearrangement. The conversion of benzophenone oxime under the influence of acetyl chloride was formulated by Kuhara as follows:

$$
\underset{\underset{\text{NOH}}{\parallel}}{C_6H_5CC_6H_5} + CH_3COCl \xrightarrow{\text{rapid}} \left[\underset{\underset{\text{HNOCOCH}_3}{\parallel}}{C_6H_5CC_6H_5} \right] Cl^- \xrightarrow{\text{slow}}
$$

$$
\left[\underset{\underset{\text{HNC}_6H_5}{\parallel}}{C_6H_5COCOCH_3} \right]^+ Cl^- \xrightarrow{\text{rapid}} \underset{\underset{\text{HNC}_6H_5}{|}}{C_6H_5CO} + CH_3COCl
$$

Here, the amount of oxime converted into benzanilide was independent of the quantity of acetyl chloride used, provided this was in excess.

Kuhara's formulations of the transformations are by no means consistent, but the implication in the case of the acetate is that salt formation is a necessary prerequisite to rearrangement and that the ester of a weak acid rearranges only in the form of its salt. When the pure oxime acetate was treated with less than the equivalent of hydrogen chloride, the quantity of ester rearranged was proportional to the amount of acid used, while with an excess of hydrogen chloride it was proportional to the quantity of ester. Precisely what does occur during the rearrangement of the acetate in the presence of hydrogen chloride is not clear. The ion itself may rearrange; on the other hand, the salt of the ester may break down to give the oxime hydrochloride, which then rearranges in accordance with Chapman's mechanism (7) for ketoxime hydrochlorides. In this connection it is significant that the only product isolated

TABLE 1

Rearrangement of benzophenone oxime to benzanilide by acid chlorides

$T = 60°C.$

TIME	PERCENTAGE BENZANILIDE		
REAGENT......	$C_6H_5SO_2Cl$	$CH_2ClCOCl$	CH_3COCl
minutes			
10	93.2	61.0	0.0
30		66.1	9.4
60		70.7	26.9
90		74.9	37.2
120		76.9	43.9

and characterized by Kuhara from the rearrangement of benzophenone oxime acetate in the presence of hydrogen chloride was benzanilide.

At the time Kuhara was carrying out his investigations of the rearrangement, Meisenheimer's elucidation (20) of the change as one involving a *trans* interchange of groups had not been made, and, regarding the transformation as one involving a *cis* interchange, Kuhara suggested that the initiating factor in the change was the tendency of the acid residue to separate from the nitrogen atom. The rearrangement was found to be facilitated by an increase in temperature, by an increase in the hydrogen-ion concentration of the medium, and also by an increase in the electron-attracting nature of the acyl group, i.e., the greater the strength of the acid corresponding to the acyl group the more facile the rearrangement. This is shown by the data in table 1, where the relative effectiveness of acetyl, chloroacetyl, and benzenesulfonyl chlorides as reagents for the conversion of benzophenone oxime to benzanilide are compared, and also by the fact that the benzenesulfonyl ester will not only rearrange spontaneously but will do so in alkaline solution, whereas the acetate requires the presence of hydrogen chloride to induce it to undergo rearrangement. Kuhara (17)

demonstrated that these rearrangements followed a unimolecular course (*cf.*
Sluiter (25)).

A further important contribution was made by Kuhara and his school (16).
From the reaction of benzenesulfonyl chloride and the sodium salt of benzo-
phenone oxime at low temperature, the benzenesulfonate (I) of the oxime
was isolated as a colorless crystalline solid; this gradually changed on standing
at room temperature, or in chloroform solution, or on exposure to ultraviolet
light to a viscous yellow ester (II). The same change occurred on melting,
but now it occurred instantaneously and with explosive violence. The ester
was unstable, and gradually changed in moist air, and instantly on treatment
with water, to benzanilide and benzenesulfonic acid.

$$C_6H_5CC_6H_5 \qquad\qquad C_6H_5COSO_2C_6H_5 \qquad\qquad C_6H_5CONHC_6H_5$$
$$\overset{\|}{N}OSO_2C_6H_5 \qquad\qquad \overset{\|}{N}C_6H_5 \qquad\qquad +\quad C_6H_5SO_3H$$

$$\text{I} \qquad\qquad\qquad\qquad \text{II}$$
$$\text{(colorless)} \qquad\qquad\qquad \text{(yellow)}$$

It was shown, moreover, that the product obtained from benzanilideimino-
chloride[2] and silver benzenesulfonate had properties similar to those of the
yellow ester (15), e.g., both exhibited the same absorption spectra.

Summarizing, it is clear that the special significance of Kuhara's work lies
in the demonstration that esters of ketoximes may undergo the Beckmann
change spontaneously and without the formation of obvious by-products.
But since the yellow intermediate products obtained from the benzenesulfonyl
derivatives were oils which could not be purified readily, and since, moreover,
it was not certain whether the original esters were entirely free from sulfonic
acid, the validity of Kuhara's view of the rearrangement could not be accepted
without reserve. The conclusion to be drawn provisionally is that the esters
of ketoximes rearrange spontaneously when the acid group is sufficiently electron-
attractive in character but, when this is not so, then salt formation as in the
case of the acetate is an essential prerequisite to rearrangement.

At this stage the study of the Beckmann change was taken up by Chapman
(10). To establish the correctness of Kuhara's view of the rearrangement
it was necessary to replace the sulfonic esters by compounds which, if they
underwent a similar change, would yield crystalline products which could
be identified with certainty, tested for purity, and estimated quantitatively.
Chapman showed that the oxime picryl ethers fulfilled these requirements and
that their rearrangement was a true Beckmann change. Benzophenone oxime
picryl ether (III) was transformed almost explosively at its melting point into
benz-*N*-picrylanilide (V), and in a suitable solvent complete change took place
without measurable by-products. In this rearrangement *N*-phenylbenzimino-
picryl ether (IV) is no doubt an intermediate product but is itself too unstable
to be isolated, for reactions which should result in its formation yield benz-*N*-

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[2] Also called benzanilideimidochloride; the name "*N*-phenylbenzimidyl chloride" is
preferred by *Chemical Abstracts*.

picrylanilide at room temperature (*cf.* Mumm, Hesse, and Volquartz (23); Chapman (5)).

$$\begin{matrix} C_6H_5 \, C \, C_6H_5 \\ \parallel \\ N \, O \, C_6H_2(NO_2)_3 \end{matrix} \quad \xrightarrow[\substack{\text{Beckmann} \\ \text{change}}]{\text{heat}} \quad \begin{matrix} C_6H_5 \, CO \, C_6H_2(NO_2)_3 \\ \parallel \\ C_6H_5 \, N \end{matrix} \quad \xrightarrow[\substack{\text{at room} \\ \text{temperature}}]{\text{rapid}}$$

III
Benzophenone oxime
picryl ether,
m.p. 107°C.

IV
N-Phenylbenzimino-
picryl ether

$$\begin{matrix} C_6H_5 \, CO \\ | \\ C_6H_5 \, N \, O \, C_6H_2(NO_2)_3 \end{matrix}$$

V
Benz-*N*-picrylanilide,
m.p. 199°C.

The picryl ether of actophenone oxime gave pure acet-*N*-picrylanilide, and the picryl and trinitro-*m*-tolyl ethers of other ketoximes underwent similar rearrangement.

In this connection it should be noted that Kuhara assigned formula VII to the rearrangement product of the sulfonyl ester (VI), but as this represents an imino ester derived from a strong acid, and as such would undergo intramolecular change to the *N*-acyl compound very readily, Chapman (10) suggested that formula VIII represents the more probable structure.

$$\begin{matrix} R \, C \, R \\ \parallel \\ N \, OSO_2 \, Ar \end{matrix} \quad \xrightarrow{\text{heat}} \quad \begin{matrix} R \, COSO_2 \, Ar \\ \parallel \\ R \, N \end{matrix} \quad \longrightarrow \quad \begin{matrix} R \, CO \\ | \\ R \, NSO_2 \, Ar \end{matrix} \quad \xrightarrow{H_2O} \quad \begin{matrix} R \, CO \\ | \\ R \, NH \end{matrix}$$

VI   VII   VIII

A kinetic study (see table 2) of the rearrangement (10) of the picryl ethers of acetophenone and benzophenone oximes in such solvents as carbon tetrachloride, benzene, chloroform, and ethylene dichloride at temperatures between 40° and 116° C. showed that the rearrangement followed a unimolecular course—the labile nature of the *N*-phenylbenziminopicryl ether ensuring that the values obtained represent the velocity of the Beckmann change. Plotted against $1/T$, the values of log k fell on a straight line, and gave for both oximes in the various solvents values of the activation energies varying from 25.5 to 28.5 kg. per gram-mole.

It should be noted that these and similar measurements represent the first occasion on which the velocity of the Beckmann change has been measured with certainty (*cf.* Sluiter (25) and Kuhara (17)). They provide also an elegant confirmation of Kuhara's view that the rearrangement of ketoximes involves, at least in certain instances, the formation of an ester of the type $R_2C{=}NOX$, which subsequently undergoes a spontaneous intramolecular change to give the anilide RCONHR when the group OX has, as in the picryl ethers, a sufficient attraction for electrons.

Further investigation (10) showed that the transformation of the oxime picryl ethers in solution did not require an external catalyst, except in so far as the solvent might be regarded as such, nor was it affected by the action of light. The effect of the solvent on the rate of change, however, was striking. The rate increased in the same order as the cohesions, the dipole moments, and the dielectric constants of the solvents, i.e., for ethylene dichloride, chloroform, and carbon tetrachloride as solvents, in the order $C_2H_4Cl_2 > CHCl_3 > CCl_4$. The transformation is clearly one which is facilitated by an environment of polar molecules.

To test this further a detailed investigation of the kinetics of the rearrangement of benzophenone oxime picryl ether in the non-polar solvent carbon tetrachloride was made (6). It was found that the concentration of the solution had an important influence on the rate of change—an increase in concentration producing an increase in the speed of rearrangement. This suggests that the oxime ether, which contains strongly polar groups, is itself functioning as a catalyst, and since the unimolecular velocity coefficient remained constant throughout the course of any individual measurement, that the catalytic activities of the oxime ether and of its changed product must be approximately equal.

TABLE 2

Rearrangement of benzophenone oxime picryl ether into benz-N-picrylanilide in chloroform at 50°C.

Time (minutes)	30.5	60	90	120	180	240	
Per cent changed	25.5	41	56	66	82	90	
$k \times 10^3$	4.2	3.8	3.95	3.9	4.15	4.1	Mean 4.0

Since the velocity coefficients at any one temperature fell upon a straight line when plotted against the concentration, it follows that at any one concentration the observed velocity is the algebraic sum of (1) the velocity of the change at infinite dilution, and (2) an additional velocity, proportional to the concentration of the solution, which is to be attributed to the catalytic effect of solute molecules; that is, $k = k_0 + xc$, where k_0 is the velocity coefficient at infinite dilution, and x is the increase of velocity for a concentration of 1 gram-mole per liter.

The velocity coefficients, moreover, indicated that at infinite dilution the molecules of the oxime ether could be activated by collision with solvent molecules alone. Values of log (k_0/η) plotted against $1/T$ fell on a straight line and gave a value of 30,250 calories per gram-mole for the energy of activation. The observed rates of change, however, were approximately twenty times as great as those calculated from this value of E, showing that in practice the critical increment had a much lower value. Again plotting the values of log x against $1/T$ a straight line was obtained; its slope corresponded to a value of E of 22,600 calories per gram-mole. To account for this large difference in the critical increments, Chapman (6) suggested that a molecule of the oxime ether can be more easily activated and rearranged when it is in the neighborhood

of another ether molecule (or of its change product) than when it is surrounded solely by molecules of an inert solvent.

Whilst, therefore, it is shown that the oxime ether can rearrange slowly when surrounded by non-polar molecules of a solvent, the rearrangement will occur with increasing facility as the collisions between polar molecules of the oxime ether and others of the same type (or molecules of the change product) become more and more frequent as the concentration increases.

If this view of the catalysis be correct, then the addition of foreign polar molecules of any kind should accelerate the rate of change, and in the same order as the strengths of their dipoles. Confirmation of this was obtained when

FIG. 2. Catalytic effects of polar solvents on the rearrangement of benzophenone oxime picryl ether in carbon tetrachloride (reference 6, p. 1552).

various polar solvents were added to a standard solution of the oxime ether in carbon tetrachloride (6). The catalytic effects of the polar solvents which contain one principal dipole fell as shown in figure 2.

Apart from irregularities observed with large concentrations of the more highly polar catalysts, when their effects increased with rising concentration more rapidly than would be consistent with a linear relationship, the velocity of the transformation could be connected with the concentration (C) of the catalyzing solvent by the empirical equation

$$k = k_{un.} + xC + yC^2$$

where $k_{un.}$ is the velocity in the absence of catalyst.

This hypothesis of catalysis by the electrical field of polar solvents was subjected to yet another test. Compounds which contain two equal and opposite dipoles in the molecule, and are therefore non-polar, should function

as catalysts provided the dipoles are sufficiently far apart for them to act independently. On the other hand, when the dipoles are close together they may be expected to neutralize each other as far as any external field is concerned. In agreement with this line of argument, p-dichlorobenzene and cis-1,4-dibromocyclohexane function as catalysts, while trans-dichloroethylene is ineffective (6).

While these kinetic studies throw a great deal of light on the general character of the rearrangement and the function of the reagent, they leave unanswered the question of the precise manner in which the picryloxy and the hydrocarbon groups migrate between the nitrogen and the carbon atoms in the rearrangement. Some degree of dissociation of the original linkages must occur, and the amount of energy necessary to bring about this dissociation will largely determine

TABLE 3

PICRYL ETHER OF...		BENZOPHENONE OXIME	p-CHLOROBENZOPHENONE		DI-p-CHLORO-BENZOPHENONE OXIME
			α-Oxime	β-Oxime	
Hydrocarbon group {migrating....		C_6H_5	C_6H_5	p-C_6H_4Cl	p-C_6H_4Cl
{stationary...		C_6H_5	p-C_6H_4Cl	C_6H_5	p-C_6H_4Cl
t........		100.5°C.	99.8°C.	100.8°C.	100°C.
$k_0 \times 10^5$........		36.4	15.4	7.74	3.24
E (calories per gram-mole)........		29,200	30,800	30,200	31,500

PICRYL ETHER OF..............		PHENYL p-TOLYL KETONE		DI-p-TOLYL KETOXIME
		α-Oxime	β-Oxime	
Hydrocarbon group {migrating.......		C_6H_5	p-$C_6H_4CH_3$	p-$C_6H_4CH_3$
{stationary.......		p-$C_6H_4CH_3$	C_6H_5	p-$C_6H_4CH_3$
t........		75.6°C.	75.3°C.	70.3°C.
$k_0 \times 10^5$........		7.47	19.5	55.1
E (calories per gram-mole)........		26,500	28,300	25,800

the ease with which migration takes place. But the migrating group is never kinetically free. If it were, then an optically active ketoxime CHRR′C(CH₃)═NOH, in which the migrating group is linked to the rest of the molecule by an asymmetric carbon atom, would undergo racemization during its transformation to the substituted acetamide, CHRR′NHCOCH₃. That this does not occur is shown by the demonstration by Kenyon and Young (13) that the oxime of (−) methyl γ-heptyl ketone retained its optical activity in the course of its conversion into (+) aceto-γ-heptylamine. Electron sharing between the asymmetric migrating group and the remainder of the molecule must therefore be continuous throughout the rearrangement. This important new evidence, which incidentally illustrates the part studies of optical activity can play in the elucidation of reaction mechanism, strengthens the view previously held that the Beckmann transformation of ketoximes is best regarded as intramolecular in character.

In an attempt to define more clearly the internal mechanism of the trans-

formation, an investigation of the effects of substitution upon the rate of rearrangement of oxime picryl ethers and upon the energy of activation was made by Chapman and Fidler (9). The velocity was found to be very susceptible to the polar nature of the substituents: introduction of an electron-attracting chlorine atom into the phenyl group of the original oxime retarded the rearrangement, whereas the electron-repelling methyl group accelerated it. Furthermore, a substituent in the migrating nucleus had a much greater effect on the rate of change than it had in the stationary nucleus. The energies of activation also showed a considerable variation from the slowest to the fastest reaction, and, apart from minor anomalies in the oximes of isomeric monosubstituted ketones, the variations in E were of the order to be expected if the differences in the rates of transformation arise essentially from differences in the energy of activation. Table 3 summarizes the salient data. Here, only one value of the velocity coefficient is recorded for each picryl ether. In practice values were obtained at four temperatures over a range of about 30°C., so that the energies of activation could be calculated with a reasonably high degree of accuracy.

An interesting feature of the effects of chloro substitution in the phenyl nucleus on the velocity of rearrangement is that these are strictly additive. This is the only case investigated in which the measurements were sufficiently accurate to justify a fully quantitative analysis. With methyl as substituent experimental difficulties made it impossible to obtain accurate data, and it is not surprising therefore that the additivity is less apparent.

CHLORO COMPOUNDS				METHYL COMPOUNDS			
$10^4/T$	26	27	28	$10^4/T$	28	29	30
$A = \dfrac{k_0 \text{ (unsubstituted)}}{k_0 \text{ (α-chloro)}}$	1.90	2.04	2.45	$A = \dfrac{k_0 \text{(unsubstituted)}}{k_0 \text{ (α-methyl)}}$	0.41	0.36	0.32
$B = \dfrac{k_0 \text{ (unsubstituted)}}{k_0 \text{ (β-chloro)}}$	4.57	4.68	5.00	$B = \dfrac{k_0 \text{(unsubstituted)}}{k_0 \text{ (β-methyl)}}$	0.13	0.12	0.12
$A \times B$...............	8.71	9.55	11.7	$A \times B$...............	0.051	0.045	0.038
$C = \dfrac{k_0 \text{ (unsubstituted)}}{k_0 \text{ (dichloro)}}$	8.51	9.55	11.5	$C = \dfrac{k_0 \text{(unsubstituted)}}{k_0 \text{(dimethyl)}}$	0.036	0.031	0.026

The demonstration of an additive relationship in this rearrangement is of particular interest in view of the earlier discovery of similar relationships in the nuclear chlorination of a wide range of aromatic ethers (Bradfield and Jones (4); Jones (12)).

The scope for substitution in the picryl group was limited by the over-riding necessity to preserve its powerful electron-attracting character sufficiently for rearrangement to occur at a conveniently measurable rate. Only one case was fully investigated: the introduction of methyl to give the 2,4,6-trinitro-

m-tolyl group lowered the rate of rearrangement and raised the energy of activation by an approximately equivalent amount. The values of E in calories per gram-mole were 29,200 and 32,100, respectively.

From the accumulated data relating to the transformation it is possible, following Kuhara and Chapman, to formulate in general outline a mechanism for the rearrangement of ketoximes. First in the sequence of reactions is the formation from the oxime and the reagent of a compound of the type

$$\begin{array}{ccc} R & & R' \\ \diagdown & & \diagup \\ & C & \\ & \parallel & \\ & N & \\ & & \diagdown \\ & & OX \end{array}$$

followed, when the group OX exerts a sufficiently powerful attraction for electrons, by a spontaneous isomeric change to give the compound

$$\begin{array}{c} R' \\ \diagdown \\ \quad\quad C\!\!=\!\!NR \\ \diagup \\ XO \end{array}$$

which yields the amide R'CONHR on subsequent hydrolysis. The initiating factor in this change is the tendency of the group OX to dissociate as anion. This withdrawal of electrons from the nitrogen creates in the $\overset{\delta+}{N}$—$\overset{\delta-}{O}$ bond a dipole with its positive end on the nitrogen atom. Because of the configuration of the oxime ester molecule, the field of this dipole is so oriented as to include the electrons of the bond R—C on the far side of the nitrogen atom within its influence, but hardly those of C—R' on the near side. When the molecule, already in this state of stress, acquires enough energy, rearrangement takes place, the group R becoming anchored to the nitrogen atom and OX migrating in compensation at the same instant to the central carbon atom. Such an interpretation appears to be in agreement with all the data relating to the rearrangement. It provides for the fact that the structure of the change product is determined solely by the spatial configuration of the oxime, and for the retention of optical activity during the rearrangement of optically active ketoximes, since it visualizes the endowment of the migrating group with its full octet of electrons throughout the transference. It accounts also for the influence of polar substituents in the groups R and R'. For instance, an electron-repelling substituent situated in the group R should facilitate the rearrangement by increasing the electron density in the bond R—C. In R' the same substituent should be less effective. This is borne out by the data relating to the methyl group as substituent.

This formulation resembles in essentials the earlier one due to Mills (21), but (a) it emphasizes the importance of the strong electron attraction of the

group OX, and (b) it assigns to the union of the nitrogen atom and the group R a more important place among the factors which determine the ease of rearrangement. Were the rate of change determined entirely by the polarization of the N—O link, or by the attraction of OX for the central carbon atom, then the effects of substituents in the groups R and R' would be more nearly equal instead of being markedly different.

Watson (30) gives a similar but more detailed analysis of the possible electronic processes concerned in the rearrangement. Electron sharing between the

FIG. 3. Velocity of the Beckmann rearrangement of benzophenone oxime—effect of hydrogen chloride as catalyst (reference 7, p. 1224):

Curve   I.   0.42 mole HCl: starting from pure oxime.
Curve II.   0.42 mole HCl: starting from 30 per cent anilide, 70 per cent oxime.
Curve III.   0.41 mole HCl + 0.002 mole benzanilideiminochloride.
Curve IV.   0.002 mole benzanilideiminochloride.

migrating hydrocarbon radical R and the rest of the molecule is again visualized as being continuous, with R carrying its full complement throughout the change.

From these researches of Kuhara and Chapman it is clear that the action of most of the reagents which bring about the Beckmann transformation of ketoximes can be accounted for by the formation of an ester, $R_2C{=}NOX$, followed by its spontaneous rearrangement when the group OX exerts a sufficient attraction for electrons as in the benzenesulfonyl esters and the picryl ethers. On the other hand, hydrogen chloride, which is known to be an effective and energetic reagent for the transformation, cannot be reconciled with this view of the mechanism, since Stieglitz and Peterson (27) and Peterson (24) showed that the esters $R_2C{=}NCl$ do not undergo rearrangement. A reinvestigation, under conditions which allowed of a quantitative study of the rearrangement

of benzophenone oxime in ethylene dichloride solutions of hydrogen chloride at 100°C., was therefore undertaken by Chapman (7). The transformation was shown to be complex: the rate was dependent on the concentration of the hydrogen chloride, but the general shape of the time–rearrangement curve was the same over a wide range of concentration. An initial period of low reactivity was followed by a steady rise until approximately 30 per cent of the oxime had been rearranged, when a rapid change at almost constant speed was maintained until the conversion was complete, the product being almost pure benzanilide. Such behavior suggests autocatalysis (curve I in figure 3).

An initial period of slow but gradualy increasing reactivity was also observed when the hydrogen chloride was introduced as oxime hydrochloride, proving that delay in the formation of this compound was not the cause of the initial low velocity. On the other hand, the presence at the outset of benzanilide (the change product) reduced the initial slow period. A mixture of 70 per cent oxime and 30 per cent benzanilide not only showed an initial slow period of short duration, but this was followed immediately by a rapid reaction identical in form with the rapid phase of the rearrangement of the pure oxime. Replacement of some of the solvent by ethyl alcohol completely inhibited the transformation.

These observations suggest that the rearrangement is accomplished through the agency of some compound which is formed from the benzanilide produced in the slow first stage, and which can be destroyed or inhibited by ethyl alcohol. Such a compound is benzanilideiminochloride, for the formation of which from hydrogen chloride and benzanilide there is some evidence (Stephen and Bleloch (26)).

$$C_6H_5CONHC_6H_5 + HCl \rightleftarrows C_6H_5C(Cl){=}NC_6H_5 + H_2O$$

Under standard conditions it was found that the addition of 0.002 mole of benzanilideiminochloride had a powerful effect on the reaction (curve III); it completely abolished the slow period and the rearrangement progressed throughout at approximately the same speed as the rapid phase of curve I. In the presence of hydrogen chloride larger amounts of the iminochloride accelerated the rate until it became too rapid for measurement. On the other hand, in the absence of hydrogen chloride 0.002 mole of the iminochloride converted only 10 per cent of the oxime to the anilide (curve IV). It appears, therefore, that for the rapid and complete transformation of the oxime into benzanilide both reagents are necessary.

From these results Chapman (7) concluded that the Beckmann rearrangement of benzophenone oxime in the presence of hydrogen chloride proceeds by the following series of reactions:

(1) The slow production of a small quantity of benzanilide.

(2) The conversion of a trace of the benzanilide into benzanilideimino-chloride by hydrogen chloride:

$$C_6H_5CONHC_6H_5 + HCl \rightarrow C_6H_5C(Cl){=}NC_6H_5 + H_2O$$

(3) The condensation of the oxime and the iminochloride to form the oxime ether:

$$(C_6H_5)_2C\!=\!NOH \;+\; C_6H_5C(Cl)\!=\!NC_6H_5$$

$$\rightarrow (C_6H_5)_2C\!=\!NOC(C_6H_5)\!=\!NC_6H_5 + HCl$$

(4) The conversion of this oxime ether into the cation:

$$(C_6H_5)_2C\!=\!NOC(C_6H_5)\!=\!NC_6H_5 + H^+ \rightarrow (C_6H_5)_2C\!=\!NOC(C_6H_5)\!=\!\overset{+}{N}HC_6H_5$$

The positively charged nitrogen atom in this cation, like the picryloxy group in the oxime picryl ethers, endows the radical $-OCC_6H_5\!=\!\overset{+}{N}HC_6H_5$ with strong electron-attracting properties and thereby enables it to initiate the rearrangement to an imido ether type of compound which, in the presence of an excess of hydrogen chloride, may undergo two alternative reactions (a or b). The series of reactions can be formulated as follows:

$$(C_6H_5)_2C\!=\!NOH \;+\; C_6H_5C(\!=\!NC_6H_5)Cl \rightarrow$$

Process (a) would lead to the formation of benzanilide and benzanilide-iminochloride, which may enter into further reaction with the oxime, while process (b) yields benzoyl-s-diphenylbenzenylamidine by a process analogous to the transformation of *N*-phenylbenziminopicryl ether into benzylpicrylaniline.

If the decomposition process (a) predominates over (b), then the above scheme accounts satisfactorily for the catalytic effect of the iminochloride, while the alternative process (b) furnishes reason for the presence of a small quantity of s-diphenylbenzenylamidine in the benzanilide obtained when benzophenone oxime hydrochloride undergoes rearrangement on heating.

This mechanism of the rearrangement of benzophenone oxime in the presence

of hydrogen chloride was tested and confirmed by the examination of the essential intermediate compound $(C_6H_5)_2C{=}NOC(C_6H_5){=}NC_6H_5$, formed from benzophenone oxime and benzanilideiminochloride. Treated with aqueous hydrogen chloride it was converted rapidly and quantitatively into benzanilide; with an excess of dry hydrogen chloride in ether it gave a mixture of benzanilide and benzanilideiminochloride; while in ether containing a trace of sulfuric acid it yielded the alternative product benzoyl-s-diphenylbenzenylamidine by process (b). Finally, its catalytic effect on the transformation of benzophenone oxime by hydrogen chloride was precisely the same as that of an equivalent amount of benzanilideiminochloride.

The rapid Beckmann rearrangement of ketoximes under the influence of hydrogen chloride as a reagent is thus seen to fall into line with the spontaneous change of the oxime ethers and esters, since it is due to the spontaneous rearrangement of an oxime derivative which is similar in nature to the ester of a strong acid.

This mechanism provides a satisfactory picture of the rearrangement once the first trace of benzanilide has been formed, but it offers no explanation of the slow consecutive reaction (curve I, figure 3) during which the requisite trace of benzanilide is actually formed. A mechanism for the slow production of benzanilide has been suggested by Bennett (see reference 8, p. 1226). This takes into account the fact that the salt of an oxime should contain both ammonium and oxonium forms in equilibrium. Now, although the proportion of the oxonium form may be exceedingly small, the group $\overset{+}{O}H_2$ would attract electrons powerfully—more so even than the picryloxy or benzenesulfonyl groups. As a result, the oxonium ion would readily undergo the Beckmann change:

$$\underset{\underbrace{\overset{+}{X^-}}}{\underset{HNOH}{\overset{RCR}{\|}}} \rightleftarrows \underset{\underbrace{X^-}}{\underset{\overset{+}{N}-\overset{H}{\underset{H}{O}}}{\overset{RCR}{\|}}} \rightarrow \left. \underset{RN}{\overset{RC-\overset{+}{O}\diagup^{H}}{\|}}\diagdown_H \right\} X^- \rightarrow \underset{\underset{\underset{RCONHR}{\updownarrow}}{RN}}{\overset{RCOH}{\|}} + HX$$

If this be so, it follows that any sufficiently strong acid should be capable of inducing the rearrangement of a ketoxime, but on account of the minute amount of oxonium salt that would be present the rate of change would of course be slow. Direct experimental confirmation of this has been provided, using picric acid as the agent for producing the transformation. In nitromethane solution benzophenone oxime gave benzanilide; no benz-N-picrylanilide could be detected (6). The above suggestion accounts satisfactorily also for the rearrangement of benzophenone oxime in aqueous acid solution (Lachmann (19)), and has the merit that it brings the outstanding apparent exceptions

into that general scheme of the Beckmann rearrangement which includes the spontaneous transformation of esters and oxime ethers.

It is clear, therefore, that the Beckmann rearrangement of benzophenone oxime by hydrogen chloride is complex, with two distinct processes operating consecutively: (1) a very slow change to benzanilide brought about by the acid reagent—in this the anilideiminochloride type of compound is not an intermediate—and (2) a much more rapid transformation starting immediately a trace of benzanilide has been formed by the first process, and occurring through a series of recognizable intermediate products. This second process accounts for the greater part of the rearrangement.

These studies of the kinetics and mechanism of the transformation of ketoximes reveal for the first time certain definite general characteristics of the change, which may be summarized as follows:

(1) The essential unity of the rearrangement. The transformation of ketoximes under the influence of various reagents depends on the intermediate formation of an ester-like compound which is capable of undergoing spontaneous rearrangement. The ease with which these esters, ethers, and salts undergo rearrangement is determined by the capacity of the radical attached to the nitrogen atom to attract electrons; the more powerful this attraction, the more facile the change.

(2) There is no evidence that the spontaneous transformation of such compounds involves any actual dissociation into free ions, although the effect of polar molecules on the velocity of rearrangement suggests that some partial dissociation occurs as a preliminary to rearrangement. The retention of optical activity during the conversion of optically active ketoximes shows, however, that the migrating hydrocarbon group is never kinetically free. The change is best regarded as intramolecular in nature.

(3) A picture of the mechanism of the rearrangement can be drawn along the lines developed by Kuhara and Mills as elaborated by Chapman and Watson.

It is clear from this brief review that although much has been achieved in recent years, more needs to be discovered before the mechanism of this Mona Lisa of molecular rearrangements is fully understood. Further investigation of other 'exchange' rearrangements would probably disclose resemblances and perhaps contribute materially to the elucidation of their characters.

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THE CHEMISTRY OF THE AMIDINES

R. L. SHRINER AND FRED W. NEUMANN[1]

Chemistry Laboratory, Indiana University, Bloomington, Indiana

CONTENTS

1. INTRODUCTION

Amidines are monacid bases characterized by the structural grouping:

$$R-\overset{\overset{\displaystyle NR'}{\|}}{C}-N\overset{\displaystyle R''}{\underset{\displaystyle R'''}{\big\langle}}$$

This review will be limited to the simple amidines in which R, R', R'', R''' are hydrogen, alkyl or aryl radicals and their substitution products. Molecules in which the two nitrogen atoms are part of a heterocyclic structure, or are

attached to elements other than hydrogen or carbon, will not be considered except when such compounds are formed as reaction products from simple amidines.

II. NOMENCLATURE AND CLASSIFICATION

Amidines have been designated as carbazylic acids, acid amidines, ammono-carboxylic acids, amimides, and imidoamides. The nomenclature used to designate specific amidines has varied somewhat; in this review the systems employed in *Chemical Abstracts* will be used in naming these compounds. In general, an amidine is named after the acid or amide which may be obtained from it by hydrolysis; thus $CH_3C(=NH)NH_2$ is *acetamidine*. The consecutive carbon atoms adjacent to the amidine carbon atom are designated in the same manner as those adjacent to a carbonyl group (α, β, γ, δ, ... etc.); thus $C_6H_5CH_2CH_2C(=NH)NH_2$ is named *β-phenylpropionamidine*. The two nitrogen atoms are referred to as N and N'; $C_6H_5C(=NCH_3)NHCH_3$ is *N,N'-dimethyl-benzamidine*. The imino nitrogen and amino nitrogen atoms are not differentiated by this system. In cases where the compound is difficult to name as a derivative of an acid, the amidine group is referred to as *carboxamidine*. For example, $NH_2C(=NH)(CH_2)_{12}C(=NH)NH_2$ may be named *dodecane-1,12-dicarboxamidine* and

$$\underset{H_2NC}{\overset{\overset{\displaystyle NH}{\|}}{}}\diagdown\!\!\!\diagup CH=CH\diagdown\!\!\!\diagup \overset{\overset{\displaystyle NH}{\|}}{CNH_2}$$

frequently called *p,p'-diamidinostilbene*, is more properly named *stilbene-4,4'-dicarboxamidine*.

The nomenclature of two types of compounds which are important intermediates in the synthesis of amidines may also be mentioned. The products obtained by the addition of alcohols to nitriles have been called imino ethers, imido ethers, imino esters, and imido esters. According to the *Chemical Abstracts* system these compounds are esters of imidic acids and are named after the parent acid. Two examples are:

$$\underset{C_6H_5\,COC_2H_5}{\overset{\overset{\displaystyle NH\cdot HCl}{\|}}{}} \qquad\qquad \underset{CH_3\,COC_2H_5}{\overset{\overset{\displaystyle NCH_3\cdot HCl}{\|}}{}}$$

Ethyl benzimidate   Ethyl N-methylacetimidate
hydrochloride   hydrochloride

The compounds commonly called imino chlorides or imido chlorides are more properly named as the acid chlorides derived from the imidic acids. For example:

$$\underset{CH_3\,COH}{\overset{\overset{\displaystyle NH}{\|}}{}} \qquad\qquad \underset{CH_3\,CCl}{\overset{\overset{\displaystyle NH}{\|}}{}} \qquad\qquad \underset{C_6H_5\,CCl}{\overset{\overset{\displaystyle NC_6H_5}{\|}}{}}$$

Acetimidic   Acetimidyl N-Phenylbenzimidyl
acid   chloride   chloride

Amidines may be classified into five general types depending on the number and distribution of the substituents on the nitrogen atoms.

A. Unsubstituted.....................R—C$\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\big\langle}}$

B. Monosubstituted..................R—C$\overset{\displaystyle NR'}{\underset{\displaystyle NH_2}{\big\langle}}$ $\rightleftharpoons$ R—C$\overset{\displaystyle NHR'}{\underset{\displaystyle NH}{\big\langle}}$

C. Symmetrical disubstituted..........R—C$\overset{\displaystyle NR'}{\underset{\displaystyle NHR''}{\big\langle}}$ $\rightleftharpoons$ R—C$\overset{\displaystyle NHR'}{\underset{\displaystyle NR''}{\big\langle}}$

D. Unsymmetrical disubstituted.......R—C$\overset{\displaystyle NH}{\underset{\displaystyle NR'R''}{\big\langle}}$

E. Trisubstituted....................R—C$\overset{\displaystyle NR'}{\underset{\displaystyle NR''R'''}{\big\langle}}$

III. PREPARATION OF AMIDINES

A. UNSUBSTITUTED AMIDINES

1. From imidic esters

Pinner in 1877 (109, 129) described the synthesis of unsubstituted amidines from nitriles *via* the imidic esters. This is still the most practical and useful method of those reported in the literature. The nitrile is dissolved or suspended in an anhydrous alcohol and treated with an excess of dry hydrogen chloride, forming an imidic ester hydrochloride. This intermediate is then caused to react with ammonia dissolved in alcohol, forming the amidine hydrochloride.

$$CH_3CN + HCl + C_2H_5OH \rightarrow CH_3C\overset{\displaystyle NH\cdot HCl}{\underset{\displaystyle OC_2H_5}{\big\langle}}$$

$$CH_3C\overset{\displaystyle NH\cdot HCl}{\underset{\displaystyle OC_2H_5}{\big\langle}} + NH_3 \rightarrow CH_3C\overset{\displaystyle NH\cdot HCl}{\underset{\displaystyle NH_2}{\big\langle}} + C_2H_5OH$$

The above method is very general: alcohols other than ethanol have been used (109), and hydrogen bromide may be substituted for hydrogen chloride. Mononitriles and dinitriles in both the aromatic and the aliphatic series have been employed (44, 85); Pinner (131) has even prepared the corresponding imidic ester hydrochloride from cyanogen. Both Pinner (109) and Gautier (54) have prepared formamidine hydrochloride from hydrogen cyanide by this method. It is not always necessary to isolate the imidic ester hydrochloride. After removal of most of the excess hydrogen chloride, ammonia may be passed into the mixture. Cyanohydrins of aldehydes and ketones also yield the desired products. Functional groups which do not react with the reagents or the expected products will not alter the course of the reactions; thus Pinner (127) was able to prepare α-carbethoxyacetamidine from ethyl cyanoacetate.

$$CH_2CN \quad \underset{COOC_2H_5}{\overset{CH_2CN}{\big|}} \rightarrow \underset{COOC_2H_5}{\overset{CH_2\overset{NH\cdot HCl}{\overset{\|}{C}}OC_2H_5}{\big|}} \rightarrow \underset{COOC_2H_5}{\overset{CH_2\overset{NH\cdot HCl}{\overset{\|}{C}}NH_2}{\big|}}$$

Also phenylaminoacetamidine may be made by this method (153):

$$C_6H_5NHCH_2CN \rightarrow C_6H_5NHCH_2\overset{NH\cdot HCl}{\overset{\|}{C}}OC_2H_5 \rightarrow C_6H_5NHCH_2\overset{NH\cdot HCl}{\overset{\|}{C}}NH_2$$

The formation of the imidic ester hydrochloride is usually carried out with no solvent other than the stoichiometric amount of the alcohol. However, Ashley and coworkers (3) have used chloroform, benzene, nitrobenzene, dioxane, or an excess of ethanol as a diluent in the preparation of imidic esters of aromatic dinitriles of higher molecular weight.

Anhydrous hydrogen chloride has been the acid most commonly used for the preparation of imidic ester salts. Other acids may be used but are not as convenient. Acid appears to be necessary for this reaction except in the special case of trichloroacetonitrile which, according to Steinkopf (154), adds methanol without halogen acid present.

$$CCl_3CN + CH_3OH \rightarrow CCl_3\overset{NH}{\overset{\|}{C}}OCH_3$$

There are several limitations as to the type of unsubstituted amidines which can be prepared by Pinner's method. Acyl cyanides such as acetyl or benzoyl cyanide can not be used (109). In an attempt to prepare the imidic ester of benzoyl cyanide the only substances isolated were ethyl benzoate and decomposition products of hydrogen cyanide.

$$RCOCN + R'OH \xrightarrow{HCl} RCOOR' + HCN$$

Pinner also found that certain ortho-substituted aromatic nitriles were unreactive with ethanol and hydrogen chloride, whereas the other position isomers

did form imidic esters which could be converted to amidines. Thus o-tolunitrile (I), 2-nitro-4-methylbenzonitrile (II), 2-amino-4-methylbenzonitrile (III), and α-naphthonitrile (IV) were recovered unchanged after treatment with the reagents, while p-tolunitrile (V) and β-naphthonitrile (VI) gave the imidic esters and amidines (118).

It is of interest to note that only one of the nitrile groups in o-phthalonitrile (VII) and in 3,4-dicyanotoluene can be converted into an imidic ester (119).

VII
o-Phthalonitrile

The other two isomeric phenylene dicyanides react to produce the expected products (132), e.g.:

$$C_6H_4(CN)_2 \longrightarrow C_6H_4(\overset{\overset{\displaystyle NH \cdot HCl}{\|}}{C}OC_2H_5)_2 \longrightarrow C_6H_4(\overset{\overset{\displaystyle NH \cdot HCl}{\|}}{C}NH_2)_2$$

m- and p-
Phthalonitriles

Not all ortho groups prevent the formation of imidic esters and amidines. The exact limitations are not known, but Pinner and Dietz (128) have prepared o-ethoxybenzamidine (VIII) by this method.

VIII
o-Ethoxybenzamidine

Other limitations of this method are due to various side reactions. Pinner (109) and Derby (39) have pointed out the instability of the imidic ester hydrochlorides. Decomposition in aqueous solution occurs as follows:

(a) $RC\overset{NH}{\underset{OR'}{\diagdown}} \longrightarrow RCN + R'OH$

(b) $RC\overset{NH}{\underset{OR'}{\diagdown}} + H_2O \longrightarrow RCOOR' + NH_3$

Reaction (b) is accelerated by hydrogen ions. Since the imidic esters are always obtained as hydrochlorides, the two steps of this method of preparing amidines must be carried out in anhydrous media. An exception to this general rule has recently been recorded. Nicotinamidine is best prepared by treatment of ethyl nicotinimidate with ammonium chloride dissolved in aqueous alcohol (8b).

Salts of imidic esters are difficult to keep, since traces of moisture will cause the above side reactions to take place. Spontaneous decomposition of the dry salts also occurs upon long standing; Derby (39) was able to demonstrate the formation of benzamide and ammonium chloride from ethyl benzimidate. Pinner (109) gives the following equation to represent the decomposition of the salts of imidic esters during recrystallization:

$$RC\overset{NH}{\underset{OR'}{\diagdown}} \cdot HCl \overset{heat}{\longrightarrow} RCONH_2 + R'Cl$$

Imidic ester hydrochlorides can form ortho esters in the presence of an excess of alcohol (136).

$$RC\overset{NH}{\underset{OR'}{\diagdown}} \cdot HCl + 2R'OH \longrightarrow RC(OR')_3 + NH_4Cl$$

The important rôle of these side reactions is reflected by the experimental procedures used and the yields obtained. Using the method of Pinner, Derby (39) employed equimolecular amounts of nitrile and alcohol, and kept the temperature of reaction at 0°C. during the formation of the imidic ester; anhydrous ether was added to the reaction mixture to facilitate the isolation of the product. However, Ashley and coworkers (3) found no evidence for the existence of unstable hydrochlorides in their work, in which they used aromatic nitriles of higher molecular weight. Thus, while more caution must be taken in the preparation of low-molecular-weight or aliphatic imidic esters, such as ethyl acetimidate, the use of aromatic nitriles allows greater flexibility in experimental conditions.

No definite mechanism for the formation of the amidine from the imidic ester has been established. Knorr (76) suggested that the reaction involved an ammonium ion. However, benzamidine may be formed by the action of alcoholic ammonia on the free imidic ester (3, 15). Perhaps the reaction mechanism is similar to that suggested for the hydrolysis of esters.

$$
\underset{\substack{\text{NH}\\ \| }}{\text{R—C—OR}} \longrightarrow \underset{\substack{\delta-\\ \text{NH}\\ | \\ \delta+}}{\text{R—C—OR}} \xrightarrow{\ :\text{NH}_3\ } \underset{\substack{\overline{\text{NH}}\\ | \\ ^+\text{NH}_3}}{\text{R—C—OR}} \longrightarrow \underset{\substack{\text{NH}\\ \| \\ \text{NH}_2}}{\text{R—C}} + \text{ROH}
$$

Representative preparatory directions using the method of Pinner may be found in *Organic Syntheses* (101), in *Die Methoden der organischen Chemie* by Houben (63), and in *Die Imidoäther und ihre Derivate* by Pinner (109).

Tafel and Enoch (157) have prepared ethyl benzimidate hydrochloride by a method different from that used by Pinner. Treatment of benzamide with silver nitrate and sodium hydroxide in aqueous solution produced a compound which turned white after standing. This white compound, silver benzamide, was caused to react with ethyl iodide, followed by treatment with anhydrous ether and hydrogen chloride. Ethyl benzimidate hydrochloride was produced, and this compound was converted into the amidine by means of ammonia; both products were identical with those obtained by Pinner's method. These workers then used other aromatic amides to show that the method was general.

$$
\text{C}_6\text{H}_5\text{CONH}_2 \rightarrow \text{C}_6\text{H}_5\text{C}\underset{\text{OAg}}{\overset{\text{NH}}{\Big\langle}} \rightarrow \text{C}_6\text{H}_5\text{C}\underset{\text{OC}_2\text{H}_5}{\overset{\text{NH}\cdot\text{HCl}}{\Big\langle}} \rightarrow \text{C}_6\text{H}_5\text{C}\underset{\text{NH}_2}{\overset{\text{NH}\cdot\text{HC}}{\Big\langle}}
$$

Mention should be made of the fact that the addition compounds of nitriles with hydrogen chloride do not produce amidines when treated with ammonia but regenerate the nitrile (152). This observation has led to the suggestion that they are salt-like complexes of the nitrile with hydrogen chloride and not true imidyl chlorides.

2. From thioamides

Bernthsen (11, 12) was the first to report the use of thioamides in the preparation of amidines. An unsubstituted aromatic or aliphatic thioamide is caused to react with concentrated ammonium hydroxide, a reaction, which sets up an equilibrium between the thioamide and amidine hydrosulfide. The addition of mercuric chloride assists in driving the reaction to completion, owing to the formation of insoluble mercuric sulfide. It is also possible that the ammonia and mercuric chloride form aminomercuric chloride (11), which then reacts with the amidine hydrosulfide.

$$\underset{\displaystyle C_6H_5\overset{S}{\overset{\|}{C}}NH_2}{} + NH_3 \rightleftarrows \underset{\displaystyle C_6H_5\overset{NH}{\overset{\|}{C}}NH_2 \cdot H_2S}{}$$

$$NH_3 \Big| HgCl_2$$

$$C_6H_5\overset{NH}{\overset{\|}{C}}NH_2 \cdot HCl + HgS + NH_4Cl$$

3. Amination of nitriles with alkali metal amides

Both aromatic and aliphatic nitriles add alkali metal amides to produce salts of amidines (10, 32, 48, 74, 178). The reaction may be carried out in anhydrous media such as benzene, toluene, xylene, anisole, or biphenyl or by reaction in liquid ammonia (32, 48). The amides of sodium, potassium, and calcium have been used. In a considerable number of cases potassium amide appears to give better yields (32).

$$RCN + KNH_2 \longrightarrow \underset{\displaystyle NH_2}{RC{=}NK}$$

The lower aliphatic nitriles undergo considerable polymerization upon treatment with sodium amide in benzene at 60–70°C.; hence, in these cases the reaction is best carried out at a low temperature in liquid ammonia. Under the latter conditions, yields of 30 to 50 per cent of potassium acetamidine, propionamidine, n-butyramidine, and n-valeramidine may be obtained. By the action of sodium amide in benzene at 60–70°C. yields of 85–90 per cent may be obtained from branched-chain nitriles (such as α,α-diethylacetamidine) or from aromatic nitriles.

The reaction fails with nitriles containing reactive methylene groups, such as phenylacetonitrile. The latter undergoes salt formation and subsequent condensation to a dimer:

$$C_6H_5CH_2CN \xrightarrow{KNH_2} \underset{\displaystyle K}{C_6H_5CHCN} \longrightarrow \underset{\displaystyle C_6H_5CHCN}{C_6H_5CH_2C{=}NK}$$

Conversion of the alkali metal salts to the amidines may be accomplished by careful hydrolysis with water (178) at a low temperature in order to avoid hydrolysis to the amide. Frequently better yields result by treatment with absolute alcoholic hydrogen chloride (32) to produce the amidine hydrochloride.

$$\underset{\displaystyle NH_2}{RC{=}NK} + H_2O \longrightarrow \underset{\displaystyle NH_2}{RC{=}NH} + KOH$$

$$\underset{\displaystyle NH_2}{RC{=}NK} + HCl \xrightarrow{C_2H_5OH} \underset{\displaystyle NH_2}{RC{=}NH \cdot HCl} + KCl$$

4. Use of nitriles and ammonium chloride

Cornell (32) has prepared benzamidine hydrochloride and aliphatic amidines in low yields by heating the corresponding nitriles in sealed tubes with ammonium chloride in liquid ammonia.

$$C_6H_5CN + NH_4Cl \xrightarrow{NH_3} C_6H_5C\begin{matrix} \nearrow NH \\ \searrow NH_2 \end{matrix} \cdot HCl$$

Bernthsen has also prepared unsubstituted amidines by this method (12). Cornell reports that no reaction occurs when only the nitrile and ammonia are used.

5. Ammonolysis of substituted amidines

Niemann has prepared benzamidine by treating N,N'-diphenylbenzamidine with an excess of ammonia (98).

$$C_6H_5C\begin{matrix} \nearrow NC_6H_5 \\ \searrow NHC_6H_5 \end{matrix} + 2NH_3 \longrightarrow C_6H_5C\begin{matrix} \nearrow NH \\ \searrow NH_2 \end{matrix} + 2C_6H_5NH_2$$

6. From triazines

Robin (138) has obtained benzamidine hydrochloride by heating 2,4,6-triphenyltriazine with hydrochloric and acetic acids at 120°C.

$$+ 4H_2O + HCl \xrightarrow{CH_3COOH}$$

$$C_6H_5-C\begin{matrix} \nearrow NH \\ \searrow NH_2 \end{matrix} \cdot HCl + NH_4Cl + 2C_6H_5COOH$$

7. From amides

A variety of methods have been reported for the preparation of acetamidine salts. Strecker in 1857 (156) made the hydrochloride by passing hydrogen chloride through molten acetamide. Fichter, Stutz, and Grieshaber (49) obtained acetamidine nitrate by heating acetamide and ammonium nitrate at 170°C. in liquid ammonia for 20 hr.

8. By hydrolysis of imidic esters

Rule (148) showed that *mandelamidine mandelate* was formed, in fair yield, by shaking ethyl mandeloimidate with water at room temperature for 5 days.

$$2C_6H_5CHOHC\overset{\displaystyle N\!H}{\underset{\displaystyle OC_2H_5}{\Big\langle}} \;+\; 2H_2O \longrightarrow$$

$$C_6H_5CHOHC\overset{\displaystyle N\!H}{\underset{\displaystyle NH_2}{\Big\langle}} \cdot C_6H_5CHOHCOOH + 2C_2H_5OH$$

This decomposition is rather unusual, but Rule found that free imidic esters prepared from other cyanohydrins reacted with water to form analogous products.

9. Miscellaneous

By heating benzoic acid and benzenesulfonamide at 225°C., Rouiller (140) prepared the benzenesulfonate of benzamidine; no reaction took place between benzamide and benzenesulfonamide under the same conditions.

$$C_6H_5COOH + 2C_6H_5SO_2NH_2 \longrightarrow$$

$$C_6H_5C(=NH)NH_2 \cdot C_6H_5SO_3H + C_6H_5SO_3H$$

Bernton (15) has reported the formation of the nitrite of phenylacetamidine by the action of a solution of sodium nitrite on ethyl phenylacetimidate hydrochloride. This unusual reaction probably occurs in the following stages:

$$C_6H_5CH_2\overset{\displaystyle N\!H\cdot HCl}{\overset{\|}{C}}OC_2H_5 + NaNO_2 + H_2O \longrightarrow$$

$$C_6H_5CH_2COOC_2H_5 + NH_4NO_2 + NaCl$$

$$C_6H_5CH_2\overset{\displaystyle N\!H}{\overset{\|}{C}}OC_2H_5 + NH_4NO_2 \longrightarrow C_6H_5\overset{\displaystyle N\!H}{\overset{\|}{C}}NH_2 \cdot HNO_2 + C_2H_5OH$$

Bernton also noted that ammonium nitrate converted ethyl phenylacetimidate into the nitrate of the amidine.

$$C_6H_5CH_2\overset{\displaystyle N\!H}{\overset{\|}{C}}OC_2H_5 + NH_4NO_3 \longrightarrow C_6H_5CH_2\overset{\displaystyle N\!H}{\overset{\|}{C}}NH_2 \cdot HNO_3 + C_2H_5OH$$

Acetamidine nitrate has been formed by the electrolysis of a mixture of ammonium carbonate, ethanol, and ammonia (49). By substitution of *n*-propyl alcohol or *n*-butyl alcohol for ethanol, propionamidine and *n*-butyramidine may be obtained. Fichter (49) also obtained acetamidine by the oxidation

of ethanol or acetaldehyde in ammoniacal ammonium nitrate solution with calcium permanganate or ammonium persulfate.

Amidoximes may be reduced catalytically or electrolytically to amidines (94).

The formation of unsubstituted amidines by the action of ammonia on ortho esters represents a possible method of preparation. Although this reaction is mentioned in a number of text books, no specific data on the reaction appear to be recorded in the literature.

$$RC(OC_2H_5)_3 + 2NH_3 \longrightarrow R\overset{\overset{\text{NH}}{\|}}{C}NH_2 + 3C_2H_5OH$$

B. MONOSUBSTITUTED AMIDINES

1. From amides

The preparation of monosubstituted amidines using N-substituted amides is one of the more common methods. The amide is first converted to the imidyl chloride, usually by treatment with phosphorus pentachloride; the halogen-substituted compound is then caused to react with ammonia. Thus Lossen (90) was able to prepare N-phenylbenzamidine.

$$C_6H_5CONHC_6H_5 \xrightarrow{PCl_5} \underset{\underset{\text{Cl}}{|}}{C_6H_5C}{=}NC_6H_5 \xrightarrow{NH_3} \underset{\underset{\text{NH}_2}{|}}{C_6H_5C}{=}NC_6H_5$$

Walther and Grossmann (172) have prepared N-phenyl-α-(p-chlorophenyl)-acetamidine from p-chlorophenylacetamide by the following reactions:

$$Cl\text{—}\langle\ \rangle\text{—}CH_2CONH_2 \xrightarrow{PCl_5} Cl\text{—}\langle\ \rangle\text{—}CH_2\underset{\underset{\text{}}{}}{\overset{\overset{\text{Cl}}{|}}{C}}{=}NH + HCl + POCl_3$$

$$Cl\text{—}\langle\ \rangle\text{—}CH_2\underset{\underset{\text{Cl}}{|}}{C}{=}NH + C_6H_5NH_2 \longrightarrow Cl\text{—}\langle\ \rangle\text{—}CH_2\underset{\underset{\text{NC}_6\text{H}_5}{\|}}{C}NH_2 \cdot HCl$$

The extension of the method to the preparation of unsubstituted amides is not satisfactory because low yields are obtained, probably because the imidyl chloride is converted to the nitrile.

2. Addition of sodium amide to Schiff bases

Kirsanov and Ivashchenko (75) reported in 1935 a new procedure for the preparation of substituted amidines. A Schiff base is treated with sodium amide in the presence of dry toluene at 120°C. Ammonia is evolved, and the residue yields monosubstituted amidines in yields ranging from 13 to 23 per cent. Although many side products are formed, no disubstituted amidines were isolated.

$$C_6H_5CH{=}NC_6H_5 \xrightarrow{NaNH_2} C_6H_5C\overset{\overset{\displaystyle /\!\!/NC_6H_5}{}}{\underset{\displaystyle \backslash NH_2}{}}$$

3. From nitriles

Both aliphatic and aromatic nitriles can be caused to react with either aryl or alkyl primary amine hydrochlorides under the influence of heat to form amidines (11, 12, 43, 149, 172).

A disadvantage of this method is that disubstituted amidines may be formed. Heating acetonitrile and aniline hydrochloride at 170°C. caused the formation of N-phenylacetamidine, while heating to 240°C. produced N,N'-diphenyl-acetamidine (11).

Lottermoser (91) and others (172) have applied this method successfully by the use of the free amine and powdered sodium. The sodium salt of the amidine, which is obtained, is converted to the free base by hydrolysis with water. N-Substituted amidines can be prepared from o-tolunitrile by this method. This is of interest because it will be recalled that o-tolunitrile did not produce o-methylbenzamidine by Pinner's method.

4. From imidic esters

Just as unsubstituted amidines are formed by the action of ammonia on imidic esters, so may monosubstituted amidines be prepared by replacing the ammonia by primary amines (90, 109).

Pinner points out, however, that higher temperatures and longer periods of reaction cause the formation of disubstituted products, probably because of the existence of the following equilibrium:

$$RC\underset{NHR'}{\overset{NH}{\Big\langle}} + R'NH_2 \underset{heat}{\rightleftarrows} RC\underset{NHR'}{\overset{NR'}{\Big\langle}} + NH_3$$

Hill and Rabinovitz (60) have used Pinner's method to prepare both mono- and di-substituted amidines.

$$CH_3C\underset{OC_2H_5}{\overset{NH}{\Big\langle}} + H_2N\langle\quad\rangle OC_2H_5$$

$$CH_3C\underset{NH_2}{\overset{N\langle\quad\rangle OC_2H_5}{\Big\langle}} + C_2H_5OH$$

$$CH_3C\underset{OC_2H_5}{\overset{NH}{\Big\langle}} \cdot HCl + 2H_2N\langle\quad\rangle OC_2H_5$$

$$CH_3C\underset{NH\langle\quad\rangle OC_2H_5}{\overset{N\langle\quad\rangle OC_2H_5}{\Big\langle}} + NH_4Cl + C_2H_5OH$$

5. From thioamides

The following equations represent the extension of Bernthsen's method of preparing unsubstituted amidines to that of monosubstituted ones (11, 12):

$$R\overset{S}{\overset{\|}{C}}NH_2 + R'NH_2\cdot HCl \longrightarrow RC\underset{NH_2}{\overset{NR'}{\Big\langle}}\cdot HCl + H_2S$$

$$R\overset{S}{\overset{\|}{C}}NHR' + NH_4Cl \longrightarrow RC\underset{NH_2}{\overset{NR}{\Big\langle}}\cdot HCl + H_2S$$

The limitations of Pinner's method should also apply to this process. *S*-Alkyl isothioamides may also be used.

6. From cyanamides

Busch and Hobein (23) have prepared several amidines by the action of the Grignard reagents on phenylcyanamide.

Phenylcyanamide was caused to react with an excess of phenylmagnesium bromide, and the addition product decomposed to yield N-phenylbenzamidine.

$$C_6H_5NHCN \xrightarrow{2C_6H_5MgBr} C_6H_5NC\overset{NMgBr}{\underset{\underset{MgBr}{|}}{\diagdown C_6H_5}}$$

$$\downarrow H_2O$$

$$C_6H_5NC\overset{NH}{\underset{\underset{H}{|}}{\diagdown C_6H_5}}$$

7. Alkylation of unsubstituted amidines

Pinner and Klein (130) prepared N-ethylbenzamidine by heating benzamidine and ethyl iodide at 100°C.

$$C_6H_5C\overset{NH}{\underset{NH_2}{\diagdown}} + C_2H_5I \longrightarrow C_6H_5C\overset{NC_2H_5}{\underset{NH_2}{\diagdown}} \cdot HI$$

Alkylation can proceed further, forming disubstituted products (134, 135).

C. SYMMETRICAL DISUBSTITUTED AMIDINES

1. From amides

Gerhardt in 1858 (55) prepared N,N'-diphenylbenzamidine by heating N-phenylbenzimidyl chloride with aniline.

$$C_6H_5\overset{Cl}{\underset{}{\overset{|}{C}}}=NC_6H_5 + C_6H_5NH_2 \longrightarrow C_6H_5C\overset{NC_6H_5 \cdot HCl}{\underset{NHC_6H_5}{\diagdown}}$$

Other early workers—Wallach (166), Bamberger and Lorenzen (7), and von Pechmann (106, 107)—have extended this reaction as a general preparation of amidines.

$$R-C-NHR' \xrightarrow{PCl_5} R-\overset{Cl}{\underset{}{\overset{|}{C}}}-NHR' \longrightarrow R-\overset{Cl}{\underset{}{\overset{|}{C}}}=NR' + HCl$$

$$R-\overset{Cl}{\underset{}{\overset{|}{C}}}=NR' + R''NH_2 \longrightarrow R-C\overset{NR'}{\underset{NHR''}{\diagdown}} \cdot HCl$$

The usual method is to first form the imidyl chloride, remove the excess reagent, and then add the amine (7, 59, 106, 166). Various workers (7, 60, 151) have prepared amidines by heating the amine and amide with about ten parts by weight of phosphorus trichloride at 110–120°C. for 3 hr.; the amidine is isolated after dissolving the reaction mixture in cold water and adding alkali. Bureš and Kundera (21) used a similar procedure, substituting phosphorus oxychloride or pentachloride for the trichloride.

It is possible to write two different isomeric formulas for a symmetrical disubstituted amidine.

$$R-C\underset{NHR''}{\overset{NR'}{\diagup}} \quad \text{and} \quad R-C\underset{NR''}{\overset{NHR'}{\diagdown}}$$

von Pechmann (105, 106, 107) in 1895 demonstrated that attempts to synthesize the two forms of such amidines produced the same compound. This fact has been confirmed by other workers (21). Thus there are usually two alternatives in the choice of amide and amine in the synthesis of a given amidine. The following equations will illustrate this point:

$$C_6H_5\overset{O}{\overset{\|}{C}}NHC_6H_5 + CH_3NH_2 \xrightarrow{PCl_5}$$

$$C_6H_5\overset{O}{\overset{\|}{C}}NHCH_3 + C_6H_5NH_2 \xrightarrow{PCl_5} C_6H_5C\underset{NCH_3}{\overset{NHC_6H_5}{\diagup}}$$

Wallach (167) prepared N,N'-di-p-tolylacetamidine by heating p-methylacetanilide and phosphorus pentachloride.

$$CH_3\overset{O}{\overset{\|}{C}}NH\langle\quad\rangle CH_3 \xrightarrow[\text{heat}]{PCl_5} CH_3C\underset{Cl}{=}N\langle\quad\rangle$$

$$\downarrow CH_3CONH\langle\quad\rangle CH_3$$

$$CH_3C\underset{NH\langle\quad\rangle CH_3}{\overset{N\langle\quad\rangle CH_3}{\diagup}} + CH_3COCl$$

Amidines may be formed by heating an aryl amine and an amide in the presence of phosphorus pentoxide or other condensing agents (150).

$$ArNH_2 + CH_3\overset{O}{\overset{\|}{C}}NHAr \xrightarrow{P_2O_5} CH_3C\underset{NHAr}{\overset{NAr}{\diagup}} + 2HPO_3$$

Disubstituted amidines may be prepared from acetanilide, its derivatives, homologs, or analogous compounds—with the exception of arylglycine anilides—by treatment with phosgene in the presence or absence of condensing agents (26).

$$2C_6H_5NHCCH_3 + COCl_2 \rightarrow CH_3C\overset{NC_6H_5}{\underset{NHC_6H_5}{\big<}} + CH_3COCl + HCl + CO_2$$

The reaction is stated to proceed smoothly and no by-products are formed.

Tobias (161) and Wallach (168) in 1882 prepared N,N'-diphenylformamidine. hydrochloride by treating formanilide with hydrogen chloride gas at 100°C. The formation is thought to take place in the following manner:

$$C_6H_5NHCHO \rightarrow C_6H_5NH_2 + CO$$

$$C_6H_5NHCHO + C_6H_5NH_2 + HCl \longrightarrow HC\overset{NC_6H_5}{\underset{NHC_6H_5}{\big<}} \cdot HCl + H_2O$$

Wallach (168) extended this method to the preparation of the corresponding acetamidine by heating acetanilide with hydrogen chloride at 150°C. N,N'-Diphenylacetamidine was made by heating acetanilide with aniline hydrochloride. N,N'-Diphenylformamidine has been prepared by heating aniline and formic acid in the presence of boric acid or a borate and (or) iron (68). The first stage of the mechanism is probably the formation of formanilide, the amidine then being formed as described above.

$$C_6H_5NH_2 + HCOOH \longrightarrow C_6H_5NHCHO + H_2O$$

2. From substituted ureas

Dains (33, 38) has shown that amidines may be prepared from symmetrical diaryl and dialkyl ureas and acid chlorides. Both aromatic and aliphatic acyl halides may be used.

$$(a)\quad RNH\overset{O}{\overset{\|}{C}}NHR + R'COCl \xrightarrow{150°C.} RNH\overset{O}{\overset{\|}{C}}NR\underset{O=C-R'}{|} + HCl$$

$$(b)\quad RNH\overset{O}{\overset{\|}{C}}-\overset{R}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}R' \longrightarrow RNHCOR' + RNCO$$

$$(c)\quad RNHCOR' + RNCO + HCl \xrightarrow{150°C.} R'C\overset{NR}{\underset{NHR}{\big<}} \cdot HCl + CO_2$$

Kuhn had previously shown (78) that benzanilide forms N,N'-diphenyl-benzamidine when heated with phenyl isocyanate.

3. From orthoformic ester

Claisen (28) and others (37, 56, 171) refluxed ethyl orthoformate and aromatic amines in an alcoholic solution to form substituted formamidines. Yields as high as 77 per cent have been reported (37). The reaction between phenetidine and orthoformic ester illustrates this method:

$$2H_2N\underset{}{\diagdown}OC_2H_5 + HC(OC_2H_5)_3 \longrightarrow$$

$$HC\diagup\overset{N\diagdown OC_2H_5}{\underset{NH\diagdown OC_2H_5}{}} + 3C_2H_5OH$$

4. From benzotrichloride

In 1865 Limpricht (88) demonstrated that N,N'-diphenylbenzamidine could be produced by the action of aniline in excess upon benzotrichloride according to the following reaction:

$$C_6H_5CCl_3 + 4C_6H_5NH_2 \longrightarrow C_6H_5C\diagup\overset{NC_6H_5}{\underset{NHC_6H_5}{}} \cdot HCl + 2C_6H_5NH_3Cl$$

Doebner (41) confirmed this observation. Joshi, Khanolkar, and Wheeler (70) modified the procedure by using nitrobenzene as a solvent to reduce the violence of the reaction; yields up to 85 per cent were obtained. The method works well with meta- and para-substituted anilines, but satisfactory results could not be obtained with benzidine and certain ortho-substituted aromatic amines.

The following mechanism has been proposed (70):

$$C_6H_5CCl_3 \xrightarrow{ArNH_2} C_6H_5\overset{Cl}{\underset{Cl}{C}}NHAr \xrightarrow{-HCl} C_6H_5\overset{}{\underset{Cl}{C}}=NAr$$

$$C_6H_5\overset{}{\underset{Cl}{C}}=NAr + ArNH_2 \longrightarrow C_6H_5C\diagup\overset{NAr}{\underset{NHAr}{}} \cdot HCl$$

If moisture is present during the reaction, a benzanilide is formed according to the reaction:

$$C_6H_5\overset{}{\underset{Cl}{C}}=NAr + H_2O \longrightarrow C_6H_5\overset{}{\underset{O}{C}}NHAr + HCl$$

5. From dialkylcarbodiimides

Busch and Hobein (23) have devised a method of preparation in which diphenyl carbodiimide and aryl or alkyl magnesium halides are used. The following equations serve as illustration:

$$RN{=}C{=}NR \ + \ R'MgBr \ \longrightarrow \ RN{=}\underset{\underset{R'}{\mid}}{C}{-}\underset{\underset{MgBr}{\mid}}{NR}$$

$$RN{=}\underset{\underset{R'}{\mid}}{C}{-}\underset{\underset{MgBr}{\mid}}{NR} \ + \ H_2O \ \xrightarrow{NH_4Cl} \ R'C\overset{\diagup NR}{\diagdown NHR} \ + \ MgClBr$$

6. From trichloroethylene

Amidines have been prepared from trichloroethylene and aromatic amines (65, 141). The two reagents are boiled with 15 per cent sodium hydroxide to produce the disubstituted amidines in yields of 60–65 per cent. The method is not general, since certain amines are unreactive and since α-aminoacetamidines are produced.

$$4C_6H_5NH_2 \ + \ \underset{\underset{Cl}{\mid}}{CH}{=}\underset{\underset{Cl}{\mid}}{CCl} \ \longrightarrow \ C_6H_5NHCH_2C\overset{\diagup NC_6H_5}{\diagdown NHC_6H_5} \ \cdot 2HCl \ + \ C_6H_5NH_3Cl$$

7. From imidic esters

The extension of Pinner's method for preparing amidines to the formation of symmetrical disubstituted amidines has been described (60, 92, 109, 111,172).

$$RC\overset{\diagup NH}{\diagdown OC_2H_5} \ \cdot HCl \ + \ 2R'NH_2 \ \xrightarrow{heat} \ RC\overset{\diagup NR'}{\diagdown NHR'} \ + \ NH_4Cl \ + \ C_2H_5OH$$

8. From thioamides

Bernthsen (12) has shown that disubstituted amidines can be prepared from N-alkylthioamides.

$$\underset{\underset{\displaystyle RCNHR'}{\|}}{S} \ + \ R''NH_2 \ \longrightarrow \ RC\overset{\diagup NR'}{\diagdown NR''} \ + \ H_2S$$

Wallach *et al.* (169, 170) have utilized *S*-alkyl isothioanilides to prepare amidines. Thus *S*-ethyl isothioacetanilide has been caused to react with various aromatic amines:

$$CH_3C\begin{array}{c} SC_2H_5 \\ \\ NC_6H_5 \end{array} + ArNH_2 \longrightarrow CH_3C\begin{array}{c} NC_6H_5 \\ \\ NHAr \end{array} + C_2H_5SH$$

9. By alkylation

Pyman (135) has studied the alkylation of monosubstituted amidines. Symmetrical disubstituted amidines can be prepared by causing amidines to react with alkyl halides, but this method is not a general, desirable one. Both the symmetrical and the unsymmetrical dimethylbenzamidines were formed when *N*-methylbenzamidine was treated with methyl iodide:

$$C_6H_5N\begin{array}{c} NCH_3 \\ \\ NH_2 \end{array} + 2CH_3I \longrightarrow C_6H_5C\begin{array}{c} NCH_3 \\ \\ NHCH_3 \end{array} \cdot HI$$

$$+ C_6H_5C\begin{array}{c} NH \\ \\ N(CH_3)_2 \end{array} \cdot HI$$

10. From isocyanates

Beckmann and Fellrath (9) have prepared *N*-phenyl-*N'*-benzylbenzamidine from phenyl isocyanate and *N*-benzylbenzaldoxime according to the following reactions:

$$C_6H_5CH{=}NCH_2C_6H_5 + C_6H_5NCO \rightarrow$$

$$\begin{array}{c} C_6H_5 \\ | \\ NH{-}CH \\ / \quad\quad \backslash \\ C_6H_5CH \quad\quad O \\ \backslash \quad\quad / \\ N{-}C \\ | \quad \| \\ C_6H_5 \ O \end{array}$$

$$\Big\downarrow NaOC_2H_5$$

$$CO_2 + C_6H_5C\begin{array}{c} NCH_2C_6H_5 \\ \\ NHC_6H_5 \end{array}$$

11. By the Beckmann rearrangement

Stephen and Bleloch (155) have found that amidines are produced during the Beckmann transformation of ketoximes when thionyl chloride, acetyl chloride, hydrogen chloride, or phosphorus pentachloride is used as the reagent. Yields as high as 20 per cent have been obtained, although the amide predominates in all cases.

The normal Beckmann transformation of ketoximes proceeds as follows:

$$
\underset{\overset{\|}{N-OH}}{R-\overset{\|}{C}-R} \xrightarrow{HCl} \underset{\overset{|}{R-N}}{R-\overset{\|}{C}-OH} \longrightarrow \underset{\overset{|}{R-N-H}}{R-C=O}
$$

Stephen and Bleloch suggest the following equations to explain the formation of symmetrical disubstituted amidines:

$$
\underset{\overset{\|}{NOH}}{R-\overset{\|}{C}-R} \xrightarrow{HCl} \underset{\overset{\|}{NR}}{Cl-\overset{\|}{C}-R} \xrightarrow{HCl} \underset{\overset{|}{NHR}}{Cl-\overset{\overset{Cl}{|}}{C}-R}
$$

$$
R-C\underset{\diagdown Cl}{\overset{\diagup NR}{}} \quad + \quad \underset{\overset{|}{NHR}}{Cl-\overset{|}{C}-R} \quad \longrightarrow \quad R-C\underset{\diagdown NR}{\overset{\diagup NR}{}} \quad + \quad HCl
$$
$$
\underset{\overset{|}{CCl_2 R}}{}
$$

$$
R-C\underset{\diagdown NR}{\overset{\diagup NR}{}} \quad + \quad 2H_2O \quad \longrightarrow \quad R-C\underset{\diagdown NHR}{\overset{\diagup NR}{}} \quad \cdot HCl + RCOOH + HCl
$$
$$
\underset{\overset{|}{CCl_2 R}}{}
$$

12. Other methods

Brunner, Matzler, and Mössmer (20) have prepared N, N'-diphenylacetamidine by heating diacetamide and aniline hydrochloride at 150°C. A similar reaction using diacetamide and o-nitroaniline hydrochloride was also carried out. The diacylamides can be prepared by heating the corresponding acid anhydride with potassium cyanate.

Symmetrical disubstituted amidines are formed by the action of alkyl hypochlorites on Schiff bases. Thus, N, N'-diphenylbenzamidine was made by the action of tertiary-amyl hypochlorite on benzalaniline in carbon tetrachloride solution (51).

Ott and Dittus (103) report that aminoamidine hydrochlorides can be prepared by the reaction of dichloroacetylene with primary amines but not with secondary amines. Since ammonia reacts with dichloroacetylene to give

chloroacetonitrile in good yields, the products formed by the action of primary amines are probably substituted α-aminoacetamidines.

When dry hydrogen chloride is introduced into an ether or benzene solution of hydrogen cyanide, a compound having the formula $C_2H_5N_2Cl_3$ ($2HCN \cdot 3HCl$) precipitates out (29). Dains has prepared symmetrical disubstituted form-amidines [HC($=$NR)NHR] by treating this compound with aromatic amines (34).

The selective oxidation of alkylidene bis-arylamines to *sym*-diarylformamidines has been studied by Wagner (165). In some cases 50 to 78 per cent yields have resulted by the use of potassium permanganate in acetone.

$$(C_6H_5NH)_2CH_2 + O(KMnO_4) \longrightarrow C_6H_5NHCH=NC_6H_5 + H_2O$$

Symmetrically substituted amidines are reported to be formed by the condensation of β-aminoanthraquinone with carbon tetrachloride and other aromatic hydrocarbons (6).

$$2ArNH_2 + CCl_4 + Ar'H \longrightarrow Ar'\overset{\overset{\displaystyle NAr}{\|}}{-}C-NHAr + 4HCl$$

D. UNSYMMETRICAL DISUBSTITUTED AMIDINES

1. From imidic esters

Pinner (109), 111, 122) and Luckenbach (92) have prepared unsymmetrical disubstituted amidines from secondary amines and imidic ester hydrochlorides.

$$RC\overset{\displaystyle NH}{\underset{\displaystyle OC_2H_5}{\diagup}} \cdot HCl + R'R''NH \longrightarrow RC\overset{\displaystyle NH}{\underset{\displaystyle \underset{\displaystyle R''}{\overset{\displaystyle |}{NR'}}}{\diagup}} \cdot HCl + C_2H_5OH$$

The R groups may be alkyl or aryl.

2. From thioamides

Bernthsen (12) has prepared N,N-dialkylated amidines by use of the appropriate thioamides and amines. The following equations illustrate this method:

$$R\overset{\overset{\displaystyle S}{\|}}{C}NH_2 + R'R''NH \longrightarrow RC\overset{\displaystyle NH}{\underset{\displaystyle \underset{\displaystyle R''}{\overset{\displaystyle |}{NR'}}}{\diagup}} + H_2S$$

$$R\overset{\overset{\displaystyle S}{\|}}{C}NR'R'' + NH_3 \longrightarrow RC\overset{\displaystyle NH}{\underset{\displaystyle \underset{\displaystyle R''}{\overset{\displaystyle |}{NR'}}}{\diagup}} + H_2S$$

3. From nitriles

Bernthsen (12) has also prepared N, N-diphenylbenzamidine by heating benzonitrile and diphenylamine hydrochloride at 180°C. The reaction mixture was extracted with water and the free amidine precipitated by the addition of ammonium hydroxide. Yields ranged from 12 to 30 per cent; acetonitrile may also be used.

$$C_6H_5CN + (C_6H_5)_2NH \cdot HCl \longrightarrow C_6H_5\overset{\overset{\displaystyle NH}{\|}}{C}N(C_6H_5)_2 \cdot HCl$$

4. From dialkylcyanamides

Adams and Beebe (1) have prepared amidines by hydrolyzing the addition products obtained from dibenzylcyanamide and alkyl- or aryl-magnesium bromides in yields as high as 75 per cent.

$$R_2NCN + R'MgBr \longrightarrow R_2NCR'$$

$$R_2N\overset{\overset{\displaystyle }{}}{\underset{\underset{\displaystyle NMgBr}{\|}}{C}}R' + 2HCl \longrightarrow R'C\overset{\diagup NH}{\diagdown NR_2} \cdot HCl + MgBrCl$$

5. By alkylation

As pointed out previously, the alkylation of N-methylbenzamidine with methyl iodide produces N,N-dimethylbenzamidine among other products. Activated aryl halides may also be used. For example, von Walther and Grossmann (172) have prepared N-p-chlorophenyl-N-2,4,6-trinitrophenyl-benzamidine from picryl chloride by the following reaction:

$$C_6H_5C\overset{\diagup NC_6H_4Cl(p)}{\diagdown NH_2} + \underset{NO_2}{\overset{Cl}{\underset{O_2N \quad NO_2}{\bigcirc}}} \quad \underset{\underset{\displaystyle NH \cdot HCl}{\|}}{\underset{\displaystyle C_6H_5C-N-C_6H_4Cl(p)}{\overset{NO_2}{\underset{O_2N \quad NO_2}{\bigcirc}}}}$$

E. TRISUBSTITUTED AMIDINES

1. From amides

There are relatively few preparations for trisubstituted amidines in the literature. The most common method is by the use of disubstituted amides and primary amines or by the use of monosubstituted amides and secondary amines (9, 17, 19, 60). The amide is first treated with phosphorus trichloride or pentachloride. The chloro compound is then treated with the appropriate amine to form the desired amidine. The intermediary halogenated amide may or may not be isolated; Hill and Rabinowitz (60) obtained amidines by heating

the amide, amine, and phosphorus halide simultaneously, whereas other workers (9, 18) carried out the preparation in two steps. The following equations indicate the generality of the method:

$$R'-\overset{\overset{\text{O}}{\|}}{C}-NR_2 + PCl_5 \longrightarrow R'-\overset{\overset{\text{Cl}}{|}}{\underset{\underset{\text{Cl}}{|}}{C}}-NR_2 + POCl_3$$

$$R'-\overset{\overset{\text{Cl}}{|}}{\underset{\underset{\text{Cl}}{|}}{C}}-NR_2 + 2R''NH_2 \longrightarrow R'-C\overset{\nearrow NR''}{\searrow NR_2} \cdot HCl + R''NH \cdot HCl$$

$$R'-\overset{\overset{\text{O}}{\|}}{C}-NHR + PCl_5 \longrightarrow R'-\overset{\overset{\text{Cl}}{|}}{C}=NR + POCl_3 + HCl$$

$$R'-\overset{\overset{\text{Cl}}{|}}{C}=NR + R_2''NH \longrightarrow R'-C\overset{\nearrow NR}{\searrow NR_2''} \cdot HCl$$

In 1932 von Braun and Weissbach studied the effect of steric hindrance in the preparation of amidines according to the following reaction (19):

$$C_6H_5C=NC_6H_5 + \overset{NHCH_3}{\underset{}{\bigotimes}}X \longrightarrow \underset{\overset{\text{Cl}}{|}}{} \overset{C_6H_5C=NC_6H_5 \cdot HCl}{\underset{NCH_3}{\bigotimes}}X$$

When the amine was methylaniline (X=H), the yield was 36 per cent. As X increased in size, the yield decreased rapidly; when X was Cl, the yield was approximately 10 per cent.

von Braun, Jostes, and Heymons found that acetanilide could be caused to react with phosphorus pentachloride to form a trisubstituted amidine in a yield of 50 per cent (18).

$$CH_3\overset{\overset{\text{O}}{\|}}{C}NHC_6H_5 + PCl_5 \longrightarrow CH_3\overset{\overset{\text{Cl}}{|}}{C}=NC_6H_5 + POCl_3 + HCl$$

$$2CH_3\overset{\overset{\text{Cl}}{|}}{C}=NC_6H_5 \overset{heat}{\longrightarrow} CH_3C\overset{\nearrow NC_6H_5}{\underset{\underset{C_6H_5}{\diagdown}N-\overset{\overset{}{}}{\underset{\underset{Cl}{|}}{C}}=CH_2}{}} + HCl$$

Wallach had previously assigned a different structure to the product (166, 167).

2. From thioamides

The use of thioamides in the preparation of amidines has been mentioned in the preceding sections. Thus, Bernthsen (11) was able to prepare trisubstituted amidines from disubstituted thioamides and primary amines.

$$\underset{\parallel}{\overset{S}{R\overset{}{C}NR_2'}} + R''NH_2 \longrightarrow RC\overset{NR'}{\underset{NR''}{\diagdown}} + H_2S$$

3. By alkylation

Pyman (135) and earlier workers (9, 17, 27) have demonstrated that trisubstituted amidines can be prepared by the treatment of disubstituted amidines with alkyl halides. N,N-Dimethylbenzamidine yields 64 per cent of the trimethyl compound when treated with methyl iodide.

$$C_6H_5C\overset{NH}{\underset{N(CH_3)_2}{\diagdown}} + CH_3I \longrightarrow C_6H_5C\overset{NCH_3}{\underset{N(CH_3)_2}{\diagdown}} \cdot HI$$

In every case of alkylation studied, Pyman recovered some unchanged amidine; in the above example, this amounted to 9 per cent.

Alkylation of symmetrical disubstituted amidines leads to the formation of two products, owing to the tautomerism of the starting material (9, 108).

$$R—C\overset{NR'}{\underset{NHR''}{\diagdown}} \rightleftharpoons R—C\overset{NHR'}{\underset{NR''}{\diagdown}}$$

$$\downarrow CH_3I \qquad \qquad \downarrow CH_3I$$

$$R-\,C\overset{NR'}{\underset{NR''}{\diagdown}}\cdot HI \qquad R—C\overset{\overset{CH_3}{\mid}{NR'}}{\underset{NR''}{\diagdown}}\cdot HI$$

$$\overset{\cdot}{C}H_3$$

If R' and R'' are greatly different in character, one derivative is formed in large excess. Pyman suggested that the alkyl group becomes attached to the less basic nitrogen atom.

IV. Properties and Reactions of Amidines

1. The basic character

Unsubstituted amidines are strong monacid bases. They form well-crystallized salts: hydrochlorides, sulfates, acetates (109); nitrates, carbonates (84);

mandelates (148); picrates and chloroplatinates (172), etc. Under certain conditions even the nitrites are stable (90).

The basic strengths of the different amidines vary with substitution. Bernthsen (12) noticed that N,N-diphenylbenzamidine is strongly basic, whereas the N,N'-diphenylbenzamidine reacts neutral to litmus in alcoholic solution. The latter is a weaker base than ammonia, because Bernthsen was able to precipitate it from a hydrochloric acid solution by the addition of ammonia; N,N-diphenylacetamidine is evidently a stronger base than ammonia, because sodium hydroxide had to be used to precipitate the free base. It can also be concluded that benzamidine and acetamidine are stronger bases than ammonia, since the hydrochlorides can be obtained directly from solutions which contain an excess of ammonia (101). A search of the literature did not reveal any quantitative studies on the relative basic strengths of amidines.

The hydrochlorides are usually obtained by the addition of hydrogen chloride gas to alcoholic or ether solutions of the bases.

$$
\underset{NH_2}{\overset{\overset{\displaystyle NH}{\|}}{RC}} + HCl \longrightarrow \underset{NH_2}{\overset{\overset{\displaystyle NH}{\|}}{RC}} \cdot HCl
$$

As with the amines, the free bases can be recovered by the use of alkali. Lossen *et al.* (90) have prepared nitrites by treating a cold aqueous solution of the amidine hydrochloride with silver nitrite:

$$
\underset{NH_2}{\overset{\overset{\displaystyle NH}{\|}}{RC}} \cdot HCl + AgNO_2 \longrightarrow \underset{NH_2}{\overset{\overset{\displaystyle NH}{\|}}{RC}} \cdot HNO_2 + AgCl
$$

Several workers have attempted to describe the chemical structure of the amidinium cation. Sidgwick (152) indicates the structure as follows, in which either nitrogen atom could be written with the double bond.

$$
\underset{NH_2}{\overset{\overset{\displaystyle \overset{+}{NH_2}}{\|}}{R-C}} \longleftrightarrow \underset{NH_2}{\overset{\overset{\displaystyle NH_2}{}}{R-C}}
$$

It would thus be a resonance hybrid of the two alternatives (isosteric with the nitro group and the carboxylate anion).

Amidines and nitriles have the ability to form benzimidazoles from *o*-phenylenediamine. Hölljes and Wagner (61) suggest that the reactions may proceed by a single essential reaction involving *hydrogen-ion catalysis*. The essential relationships may be summarized in the following scheme:

$$R-CN \xrightarrow{H^+} [R-C\equiv\overset{+}{N}H \rightleftharpoons R-\overset{+}{C}=NH]$$

$$\Big\Uparrow NH_3 \qquad\qquad \Big\Uparrow NH_3$$

$$R-C\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\diagup\diagdown}} \quad \overset{H^+}{\longleftrightarrow} \quad R-C\overset{\displaystyle NH_2^+}{\underset{\displaystyle NH_2}{\diagup\diagdown}} \qquad R-C\overset{\displaystyle NH}{\underset{\displaystyle NH_3^+}{\diagup\diagdown}}$$

Burtles and Pyman present a third point of view (22). They suggest that the imino nitrogen of amidines is the one conferring basic properties on the molecule. Imidic esters are basic, whereas unsubstituted amides are not markedly basic.

$$R-C\overset{\displaystyle NR}{\underset{\displaystyle NHR}{\diagup\diagdown}} \qquad R-C\overset{\displaystyle NH}{\underset{\displaystyle OR}{\diagup\diagdown}} \qquad R-C\overset{\displaystyle NH_2}{\underset{\displaystyle O}{\diagdown\diagup}}$$

Amidine (basic)   Imidic ester (basic)   Amide (not basic)

Thus it appears that the conversion of the two isomeric forms of an amidine (A and B) into salts may be represented as follows:

$$\overset{\displaystyle R}{\underset{}{R'-N=C-NHR''}} + H^+ \qquad \overset{\displaystyle R}{\underset{\displaystyle H}{R'-N=C-NHR''}}$$

$$\Updownarrow$$

$$\overset{\displaystyle R}{R'-NH-C=N-R''} + H^+ \qquad \overset{\displaystyle R}{\underset{\displaystyle H}{R'NH-C=N-R''}}$$

The two salts are thus identical, since the common ion is a resonance hybrid. From studies on the tautomerism of amidines, it might be concluded that resonance is likely in the salts of unsubstituted amidines and in those of symmetrically disubstituted amidines having identical groups on the nitrogen atoms. It seems likely that one of the resonance forms postulated by Sidgwick should be partially stabilized when the two nitrogen atoms contain extremely unlike groups. In this connection mention should be made of the fact that the products obtained by the action of alkyl halides on amidines are salts and that Pyman always obtained two methylation products by the action of methyl iodide on amidines containing dissimilar groups (see page 383).

2. Physical properties

Tables of data on density and refractivities for some amidines are given by v. Auwers and Ernst (4).

3. Tautomerism

A large amount of experimental evidence indicates that monosubstituted and symmetrical disubstituted amidines having different groups on the nitrogen atoms exhibit tautomerism. The mechanism of tautomerism is an intramolecular process involving proton addition and elimination.

$$
\begin{array}{cccc}
\text{H} & \text{H} \quad\rceil & \lceil \quad \text{R}' & \text{R}' \\
\overset{\centerdot}{\text{N}} & \text{N—H}\rceil & \overset{\centerdot}{\text{N}} & \text{N—H}\rceil \\
\diagup\diagdown & \diagup & \diagup\diagdown & \diagup \\
\text{R—C} & \text{R—C} & \text{R—C} & \text{R—C} \\
\diagdown & \diagdown\diagup & \diagdown & \diagdown\diagup \\
\text{N—H}\rfloor & \text{N} & \text{N—H}\rfloor & \text{N} \cdot \\
| & | & | & | \\
\text{R}' & \text{R}' & \text{R}'' & \text{R}''
\end{array}
$$

Supporting evidence for the existence of tautomerism lies in the fact that (a) a single amidine results from reactions designed to prepare the two isomerides, (b) the alkylation of an amidine yields two products, and (c) the hydrolysis of N,N'-substituted amidines produces a mixture of amides and amines.

Many authors have tried to synthesize the two isomers of a given amidine (21, 22, 30, 69, 93, 105, 106, 107), but a single substance was usually obtained. Thus, von Pechmann (106) did not obtain two different products by the following reactions for the preparation of the isomeric N-β-naphthyl-N'-methylbenzami-dines:

$$
\begin{array}{c}
\text{Cl} \\
| \\
\text{C}_6\text{H}_5\text{C}{=}\text{NCH}_3
\end{array}
+ \text{C}_{10}\text{H}_7\text{NH}_2\,(\beta) \;-\!- \;
\text{C}_6\text{H}_5\text{C}
\begin{array}{c}
\diagup\text{NHC}_{10}\text{H}_7\,(\beta) \\
\diagdown\text{NCH}_3
\end{array}
\cdot \text{HCl}
$$

$$
\updownarrow
$$

$$
\begin{array}{c}
\text{Cl} \\
| \\
\text{C}_6\text{H}_5\text{C}{=}\text{NC}_{10}\text{H}_7\,(\beta)
\end{array}
+ \text{CH}_3\text{NH}_2 \quad \cdot \;
\text{C}_6\text{H}_5\text{C}
\begin{array}{c}
\diagup\text{NC}_{10}\text{H}_7\,(\beta) \\
\diagdown\text{NHCH}_3
\end{array}
\cdot \text{HCl}
$$

von Pechmann at one time reported the preparation of the two isomeric N-p-tolyl-N'-phenylbenzamidines (104), but it was later shown (93, 105) that the two products formed a mixture in tautomeric equilibrium, it being impossible to prove the location of the hydrogen atom in the triad system.

$$
\begin{array}{cc}
\text{H} & \text{H} \\
\overset{\centerdot}{} & \overset{\centerdot}{} \\
\text{C}_6\text{H}_5\overset{\centerdot}{\text{N}}\text{—C}{=}\text{NC}_7\text{H}_7 & \text{C}_6\text{H}_5\text{N}{=}\text{C—}\overset{\centerdot}{\text{N}}\text{C}_7\text{H}_7 \\
| & | \\
\text{C}_6\text{H}_5 & \text{C}_6\text{H}_5
\end{array}
$$

Cohen and Marshall (30) attempted to form the two tautomers (IX and X) of a disubstituted amidine by the introduction of optically active bornyl groups

into the molecule. They were unsuccessful, since the two products prepared by different methods of synthesis were identical in every respect.

$$
\begin{array}{cc}
C_6H_5C\!\!\nearrow^{NC_{10}H_{17}(l)}_{\searrow NHC_6H_5} & C_6H_5C\!\!\nearrow^{NHC_{10}H_{17}(l)}_{\searrow NC_6H_5} \\
\text{IX} & \text{X}
\end{array}
$$

They also prepared *N-l*-bornyl-*N'-d*-bornylbenzamidine and demonstrated that the compound was an optically inactive meso form.

$$
\begin{array}{cc}
C_6H_5C\!\!\nearrow^{NC_{10}H_{17}(l)}_{\searrow NHC_{10}H_{17}(d)} & C_6H_5C\!\!\nearrow^{NHC_{10}H_{17}(l)}_{\searrow NC_{10}H_{17}(d)}
\end{array}
$$

The *d*-camphorsulfonic acid salt of this amidine could not be separated into two forms by repeated recrystallization.

Burtles and Pyman (22) have isolated the two tautomeric forms of the cyclic amidines 2,4-diphenylimidazole (XI) and 2,5-diphenylimidazole (XII), and have demonstrated them to be different compounds by their physical characteristics. However, the isomers formed identical salts. A consideration of the proposed structures of the amidinium cation indicates that this fact is to be expected. Thus, the structures XIII and XIV may be resonance forms; or either one of the two may be a stable form; or both XIII and XIV may be unstable, each forming a single stable resonance hybrid.

The above authors point out that the previous attempts of von Pechmann and others to synthesize the two isomeric forms of amidines have necessarily failed wherever the bases have been converted into their *salts*.

In neutral media it has been shown by Hunter and Marriott (64) that amidines containing a hydrogen on the nitrogen are associated to some extent.

This may be due to hydrogen-bonding, with resonance occurring in the dimer in a fashion similar to that observed with carboxylic acids: e.g.,

$$2R-C\begin{smallmatrix}R'\\\|\\N\\\\\\NH\\|\\R''\end{smallmatrix} \rightleftharpoons \left[\begin{array}{c} \begin{smallmatrix}R' & & R'' \\ | & & | \\ N\rightarrow H-N \\ R-C & & C-R \\ N-H\leftarrow N \\ | & & | \\ R'' & & R' \end{smallmatrix} \\ \updownarrow \\ \begin{smallmatrix}R' & & R'' \\ | & & | \\ N-H\leftarrow N \\ R-C & & C-R \\ N\rightarrow H-N \\ | & & | \\ R'' & & R' \end{smallmatrix} \end{array} \right]$$

It is also possible that dimerization could involve salt formation with resonating cations and anions: e.g.,

$$2R'-N=\overset{\overset{\textstyle R}{|}}{C}-NHR'' \qquad \left[\begin{array}{c} R'-N=\overset{\overset{\textstyle R}{|}}{C}-NHR'' \\ \dot{H} \\ \updownarrow \\ H \\ R'NH-\overset{}{C}=\overset{}{N}-R'' \\ | \\ R \end{array} \right]^{+} \qquad \left[\begin{array}{c} R'-N=\overset{\overset{\textstyle R}{|}}{C}-N-R'' \\ \updownarrow \\ R'-N-\overset{}{C}=NR'' \\ | \\ R \end{array} \right]^{-}$$

Trisubstituted amidines are not associated.

The literature contains no authentic case of the isolation of two pure tautomeric forms of a mono- or di-substituted amidine. It seems that only a strong influence operating so as to immobilize the hydrogen atom could prevent protropy. Thus, Barber (8) was able to isolate the two forms of a substituted sulfonamidine (an amidine substituted with a highly electronegative group). Form XV could easily be converted into the stable form XVI.

$$RC\begin{smallmatrix}NSO_2Ar\\\|\\\\\\OC_2H_5\end{smallmatrix} \quad + NH_3 \qquad RC\begin{smallmatrix}NSO_2Ar\\\|\\\\\\NH_2\end{smallmatrix} \quad + C_2H_5OH$$

XV

$$RC \underset{NH}{\overset{NH_2}{<}} + ArSO_2Cl \longrightarrow RC \underset{NH}{\overset{NHSO_2Ar}{<}} + HCl$$

$$XVI$$

Barber based the above structures of these isomers on the hydrolytic products.

The fact that two monoalkylated products are obtained when certain amidines are heated with methyl iodide has been explained by the existence of tautomerism. Earlier workers (107) reported that only one methylated product was isolated; but Pyman (135) has demonstrated that in all cases *two* products were formed.

4. Hydrolysis

Amidines are characterized by their relative ease of hydrolysis. Those of the type $RC(=NH)NH_2$ react with water under milder conditions than do corresponding esters, nitriles, or amides. Thus, acetamidine forms acetic acid and ammonia when an aqueous solution is heated (109).

$$CH_3C \underset{NH_2}{\overset{NH}{<}} + 2HOH \longrightarrow CH_3COOH + 2NH_3$$

By a study of the products of hydrolysis, the structures of many amidines have been determined. Markwald (93) suggests the following reaction as the first step of hydrolysis:

$$R—C \underset{NHR''}{\overset{NR'}{<}} \cdot \quad + HOH \longrightarrow \quad R—C \overset{(a) \quad NHR'}{\underset{(b) \quad NHR''}{\underset{\vdots}{=}} OH}$$

Cleavage at (a) leads to the formation of $RCONHR''$ and $R'NH_2$; cleavage at (b) would form $RCONHR'$ and $R''NH_2$. In general, amidines can be hydrolyzed to amides and amines; the nature of the products can be illustrated as follows:

$$2RC \underset{NHR''}{\overset{NR'}{<}} + 2H_2O \rightarrow R\overset{O}{\overset{\|}{C}}NHR'' + R'NH_2 + R\overset{O}{\overset{\|}{C}}NHR' + R''NH_2$$

$$RC \underset{NR_2''}{\overset{NR'}{<}} + H_2O \rightarrow R\overset{O}{\overset{\|}{C}}NR_2'' + R'NH_2$$

Dilute acid or alkali is usually employed as a catalyst to hasten the reaction. Alcohol (11) or other solvents are often used in the hydrolysis of high-molecular-

weight or insoluble amidines. The initial degradation forms the amide and amine; further breakdown of the amide into an acid and another amine depends upon the hydrolytic conditions. Thus, hydrolysis of N-phenylbenzamidine at 120°C. produced benzoic acid, aniline, benzanilide, and ammonia (91).

The ease of hydrolysis depends upon the molecular weight of the amidine as well as the degree of substitution on the nitrogen atoms. a-Phenylacetamidine forms the amide and ammonia when its aqueous solution is warmed.

$$C_6H_5CH_2C\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\Big\langle}} + HOH \longrightarrow C_6H_5CH_2C\overset{\displaystyle O}{\underset{\displaystyle NH_2}{\Big\langle}} + NH_3$$

Beckmann and Fellrath (9) found it necessary to use concentrated hydrochloric acid at 200°C. for a period of 4 hr. to effect the following change:

$$C_6H_5C\overset{\displaystyle \overset{\displaystyle CH_3}{\overset{\displaystyle |}{NCH_2C_6H_5}}}{\underset{\displaystyle NC_6H_5}{\Big\langle}} \xrightarrow{2HOH} C_6H_5COOH + C_6H_5NH_2 + C_6H_5CH_2NHCH_3$$

Bernthsen (12) hydrolyzed N,N-diphenylbenzamidine by using concentrated hydrochloric acid at 180°C. for several hours.

$$C_6H_5C\overset{\displaystyle NH}{\underset{\displaystyle N(C_6H_5)_2}{\Big\langle}} + HOH + HCl \rightarrow C_6H_5C\overset{\displaystyle O}{\underset{\displaystyle N(C_6H_5)_2}{\Big\langle}} + NH_4Cl$$

Pyman was able to hydrolyze N,N-dimethylbenzamidine by distillation with a 20 per cent solution of sodium hydroxide (135).

$$C_6H_5C\overset{\displaystyle NH}{\underset{\displaystyle N(CH_3)_2}{\Big\langle}} + 2HOH \rightarrow C_6H_5COOH + NH_3 + (CH_3)_2NH$$

However, the following two amidines were stable to this treatment:

$$C_6H_5C\overset{\displaystyle NCH_2C_6H_5}{\underset{\displaystyle N(CH_3)_2}{\Big\langle}} \qquad C_6H_5C\overset{\displaystyle NCH_3}{\underset{\displaystyle NHCH_2C_6H_5}{\Big\langle}}$$

Wagner reports that steam distillation in absence of acid or alkali does not decompose symmetrical diarylformamidines appreciably, but that they are decomposed upon basic distillation (164). N'-Phenyl-N-methyl-N-benzyl-

benzamidine was recovered unchanged after heating to 150°C. with concentrated hydrochloric acid; it was necessary to maintain a temperature of 200°C. for 3 hr. to effect hydrolysis (9).

5. Alkylation

The alkylation of amidines in which one of the nitrogen atoms is attached to an aryl group and the other to a hydrogen or alkyl, yields as main products compounds which are alkylated on the arylamine nitrogen (27, 30, 134, 135, 177). Smaller quantities of the isomeric derivatives are also obtained.

TABLE 1

R	R'	RATIO OF A AND B FORMED (A:B)
C_6H_5	CH_3	15:1
C_6H_5	H	150:1
C_6H_5	$C_6H_5CH_2$	35:1

Pyman has illustrated these facts with the experimental evidence presented in table 1 (27, 134, 135). However, both N-phenyl-N'-p-nitrophenylbenzamidine and N-methylbenzamidine yield about equal amounts of alkylation on each nitrogen (27, 135).

Pyman has considered the mechanism of the alkylation of amidines in an attempt to determine the position of the carbon–nitrogen double bond. The formation of two products could be due to the reaction of the amidine in two isomeric forms (RN=CX—NHR' and RNH—CX=NR'), or to the reaction

of a single form which becomes methylated in two different ways—by direct addition to the tertiary nitrogen and by substitution of the imino group.

Wheeler (174), Young and Crookes (177), and Burtles and Pyman (22, 135) favor mechanism A, while von Pechmann (107), Cohen and Marshall (30), and Lander (86) favor B.

Pyman's choice of mechanism A was based on the results of experiments with open-chain amidines which did not contain a mobile hydrogen atom (135). Both N,N'-dimethyl-N-phenylbenzamidine and N,N-dimethyl-N'-phenylbenzamidine gave the same quaternary ammonium salt upon treatment with methyl iodide. These results are best explained by use of mechanism A.

The results illustrated in table 1 harmonize with the assumption that the relative yields depend on the polar characteristics of the groups R and R'. Thus, the phenyl group has a greater tendency to attract electrons and should therefore tend to stabilize the double bond at the phenylamine nitrogen atom; alkylation by the addition mechanism would then produce those derivatives actually obtained. Another tendency appears to be the effect of groups such as phenyl and carboxyl

on the position of the double bond; examples are the well-known isomeric changes of β,γ- to α,β-unsaturated acids and of 1-phenyl-2-propene to 1-phenyl-1-propene.

An examination of table 1 shows that the relative basicities of the two amines RNH_2 and $R'NH_2$ are of secondary importance. Thus, the phenylamine nitrogen was alkylated to a greater extent than were the amine, benzylamine, and methylamine nitrogen atoms because of the position of the double bond. However, a study of the amounts of the secondary products in each case indicates that $C_6H_5C(=NC_6H_5)NR'CH_3$ is produced in greater proportion the stronger the basic strength of R'.

As a result of these studies, Pyman (135) concluded that:

"... the interaction of open-chain amidines with alkyl salts leads to the attachment of the alkyl group to the nitrogen atom, which is doubly linked to carbon, and leads to the conclusion that the formation of two isomeric alkyl derivatives by the action of methyl iodide upon open-chain amidines is due to the reaction of the amidine in two isomeric forms."

If Pyman's conclusions are correct, N-methyl-N'-phenylbenzamidine reacts preferably in the form A rather than B.

$$C_6H_5C\begin{array}{c} \diagup NC_6H_5 \\ \diagdown NHCH_3 \end{array} \qquad C_6H_5C\begin{array}{c} \diagup NHC_6H_5 \\ \diagdown NCH_3 \end{array}$$

$$\text{A} \qquad\qquad \text{B}$$

6. Amidines as carbazylic acids

Franklin (50) and Cornell (32) refer to amidines as carbazylic acids because they are, in the nitrogen system of compounds, analogous to carboxylic acids. Thus acetamidine is termed "ammonoacetic acid", and the various substituted amidines are considered as carbazylic acid esters. In a water solution amidines are far too weak to show acid properties, but in liquid ammonia these properties are clearly evident. Thus in the presence of liquid ammonia amidines react with the alkali metals and their amides to form metallic derivatives (10, 32, 50).

$$R-C\begin{array}{c} \diagup NH \\ \diagdown NH_2 \end{array} + K \xrightarrow{NH_3(\text{liq.})} R-C\begin{array}{c} \diagup NH \\ \diagdown NHK \end{array} + H$$

$$R-C\begin{array}{c} \diagup NH \\ \diagdown NH_2 \end{array} + KNH_2 \xrightarrow{NH_3(\text{liq.})} R-C\begin{array}{c} \diagup NH \\ \diagdown NHK \end{array} + NH_3$$

It is of interest to note that only one of the hydrogen atoms can be replaced by an alkali metal. Other metallic salts, such as the copper and silver salts, are usually formed from the potassium or sodium derivatives (32).

Substituted amidines react in a similar manner.

$$\underset{\underset{H}{|}}{\overset{\overset{NC_6H_5}{|}}{CH_3CNC_6H_5}} + KNH_2 \xrightarrow{\text{(NH}_3\text{)}} \underset{\underset{K}{|}}{\overset{\overset{NC_6H_5}{||}}{CH_3CNC_6H_5}} + NH_3$$

When dissimilar groups are attached to the nitrogen atoms it seems probable that the loss of a proton from the isomeric amidines results in resonating amidine *anions*.

$$\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{R'N{=}C{-}NHR''}} + KNH_2 \qquad \underset{\underset{R}{|}}{\overset{\overset{R}{|}}{R'N{=}C{-}NR''}} \qquad K^+ + NH_3$$

$$\updownarrow \qquad\qquad\qquad \updownarrow$$

$$\underset{}{\overset{\overset{R}{|}}{R'NH{-}C{=}NR''}} + KNH_2 \qquad \overset{\overset{R}{|}}{R'N{-}C{=}NR''}$$

The reaction of the metallic salts with water has been discussed in a previous section. Certain of the methods of preparing amidines also support the analogy of carbazylic acids to the carboxylic acids. A better analogy is found in the pyrogenetic decomposition of the carbazylic acid salts; thus, sodium salts of carboxylic acids may be fused with soda lime to produce hydrocarbons, and the alkali derivatives of amidines can be made to react as follows:

$$RC\underset{NHNa}{\overset{NH}{<}} + NaNH_2 \longrightarrow RH + Na_2NCN + NH_3$$

Substituted amidines are ammonolyzed by acid catalyst in the presence of liquid ammonia (98).

$$RC\underset{NHC_6H_5}{\overset{NC_6H_5}{<}} \xrightarrow[\text{NH}_3\text{(liq.)}]{\text{NH}_4\text{Cl}} RC\underset{NH}{\overset{NH_2}{<}} + 2C_6H_5NH_2$$

Wagner (164) has extended the analogy between amidines and carboxylic acids in a study of the closure of imidazole, pyrimidine, and oxazole rings.

7. Effect of heat

(a) *Rearrangement:* Chapman (24) discovered that amidines, when strongly heated below the decomposition point, can undergo a dynamic isomerism which involves mobile hydrocarbon radicals. *N*-Diphenyl-*N'*-*p*-tolylbenzamidine and *N*,*N'*-diphenyl-*N*-*p*-tolylbenzamidine decompose very slowly at 350°C. When the former is heated to 300°C., little change occurs; but when it is heated to 340°C. an equilibrium mixture of the two isomers is formed. An equilibrium was

indicated because similar treatment of the latter compound produced the same mixture. According to Chapman the following equilibrium exists:

(60–65 per cent)   (35–40 per cent)

This change requires much more drastic conditions than does the migration of the proton in the case of RC(=NR')NHR''. The above proportions hold only if the groups are all similar, i.e., probability is the chief factor involved. The rearrangement was shown to be *intramolecular*, and the nature of the migrating group was found to exert very little influence on the equilibrium.

(b) *Ring closure:* In the course of the work on the rearrangement of amidines, Chapman and Perrott (25) discovered an interesting ring-closure reaction. Thus N,N'-diphenyl-N-o-chlorophenylbenzamidine is transformed into 1,2,3-triphenylbenzimidazolium chloride upon heating to 200°C.

(81 per cent)

The structure of the benzimidazolium chloride was proven by its synthesis from the monobenzoyl derivative of N,N'-diphenyl-o-phenylenediamine. Likewise, treatment of the benzimidazolium salt with alkali produced the benzoyl derivative of the substituted o-phenylenediamine. Since stronger hydrolysis with alcoholic sodium hydroxide yielded N,N'-diphenyl-o-phenylenediamine, the authors deem it likely that these reactions will furnish a convenient method

for the preparation of substituted disecondary o-phenylenediamines of known constitution.

(c) *Pyrolysis:* Unsubstituted amidines decompose when strongly heated to form ammonia and the corresponding nitrile; under the conditions of pyrolysis, the resulting nitrile often polymerized to yield additional products (109).

$$RC\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\big\backslash}} \xrightarrow{\text{heat}} RCN + NH_3$$

Substituted amidines decompose to produce similar products; thus, the destructive sublimation of N-phenylbenzamidine causes the formation of benzonitrile and aniline (11).

$$C_6H_5C\overset{\displaystyle NC_6H_5}{\underset{\displaystyle NH_2}{\big\backslash}} \xrightarrow{\text{heat}} C_6H_5CN + C_6H_5NH_2$$

Formamidine hydrochloride decomposes at the relatively low temperature of 100°C., with the formation of hydrogen cyanide and ammonium chloride (54).

$$HC\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\big\backslash}} \cdot HCl \xrightarrow{100°C.} HCN + NH_4Cl$$

One of the secondary decomposition products that can be obtained from benzamidine is cyaphenine (2,4,6-triphenyl-1,3,5-triazine) (50), which is formed by trimerization of benzonitrile:

$$3C_6H_5CN \longrightarrow$$

If an aliphatic nitrile is produced by pyrolysis of the amidine, a cyanalkine may be obtained by trimerization: e.g.,

$$3CH_3CN$$

Pinner found (109) that, in the presence of acetic anhydride, amidines could be caused to decompose into the dialkylaminopyrimidines.

Other products may also be formed from the pyrolysis of amidines. Thus

the expected breakdown products of N,N-diphenylbenzamidine are diphenylamine and benzonitrile. Bernthsen was able to isolate, besides these, a small yield of 10-phenylacridine by heating the hydrochloride at 240–250°C. for 6 hr. (12, 13).

$$C_6H_5C\overset{\displaystyle NH\cdot HCl}{\underset{\displaystyle N(C_6H_5)_2}{\big<}} \xrightarrow{\text{heat}} \text{[10-phenylacridine]} + NH_4Cl$$

Pinner reported (109, 110) that succinamidine dihydrochloride was converted to the imidine hydrochloride during an attempt at recrystallization from water.

$$\begin{matrix} CH_2C\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\big<}} \\ \quad\cdot 2HCl \\ CH_2C\overset{\displaystyle NH_2}{\underset{\displaystyle NH}{\big<}} \end{matrix} \xrightarrow{\text{heat}} \begin{matrix} CH_2C\overset{\displaystyle NH}{\underset{\displaystyle NH\cdot HCl}{\big<}} \\ CH_2C\overset{\displaystyle }{\underset{\displaystyle NH}{\big<}} \end{matrix} + NH_4Cl$$

In 1943 Barber (8) reported that a sulfonyl derivative of an amidine decomposed upon heating as follows:

$$C_6H_5C\overset{\displaystyle NH}{\underset{\displaystyle NHSO_2}{\big<}} \xrightarrow{\text{heat}} C_6H_5C\overset{\displaystyle NH}{\underset{\displaystyle NH}{\big<}}\quad\overset{\displaystyle}{\underset{\displaystyle}{}} NO_2 + SO_2$$

Barber proposes the term *desulfoxylation* for the above type of decomposition and states that the reaction proceeds smoothly.

8. Ammonolysis with ammonia and amines

The existence of the following type of equilibrium at higher temperatures has been mentioned previously (109):

$$RC\overset{\displaystyle NH}{\underset{\displaystyle NHR'}{\big<}} + R'NH_2 \rightleftharpoons RC\overset{\displaystyle NR'}{\underset{\displaystyle NHR'}{\big<}} + NH_3$$

Thus by employing an excess of ammonia, Niemann (98) was able to prepare unsubstituted from substituted amidines.

Bernthsen (11) was able to convert N-phenylbenzamidine to N,N'-diphenylbenzamidine by heating with an excess of aniline at 250°C.

$$C_6H_5C\overset{NC_6H_5}{\underset{NH_2}{\big<}} + C_6H_5NH_2 \longrightarrow C_6H_5C\overset{NC_6H_5}{\underset{NHC_6H_5}{\big<}} + NH_3$$

Other derivatives of ammonia have been employed to effect the same type of reaction. Monoaryl-substituted benzamidines have been treated with phenylhydrazine hydrochloride to yield similar products (106, 172); e.g.,

$$C_6H_5C\overset{NC_6H_5}{\underset{NH_2}{\big<}} + C_6H_5NHNH_2 \cdot HCl \longrightarrow$$

$$NH_4Cl + C_6H_5C\overset{NC_6H_5}{\underset{NHNHC_6H_5}{\big<}} \rightleftharpoons C_6H_5C\overset{NHC_6H_5}{\underset{NNHC_6H_5}{\big<}}$$

Hydroxylamine reacts with amidines in the presence of acid to form amidoximes (91, 97, 109, 172).

$$RC\overset{NH}{\underset{NH_2}{\big<}} + NH_2OH + H^+ \longrightarrow RC\overset{NOH}{\underset{NH_2}{\big<}} + NH_4^+$$

$$RC\overset{NR'}{\underset{NH}{\big<}} + NH_2OH + H^+ \longrightarrow RC\overset{NHR'}{\underset{NOH}{\big<}} + NH_4^+$$

H. Muller (97) has pointed out that amidoximes can be represented by two tautomeric structures, since they are soluble in both acid and alkali.

$$C_6H_5C\overset{NHC_6H_5}{\underset{NOH}{\big<}} \rightleftharpoons C_6H_5C\overset{NC_6H_5}{\underset{NHOH}{\big<}}$$

9. Action of acid chlorides

Amidines can be caused to react with compounds containing active halogen atoms, with the elimination of halogen acid. Probably one of the better reagents to use for the preparation of derivatives of amidines is an arylsulfonyl chloride.

The amidine is treated, as in the Hinsberg reaction, with the acid chloride at or below room temperature in a neutral or alkaline medium (8, 72, 84, 99).

$$RC\begin{matrix}{}^{\nearrow NH}\\ {}_{\searrow NH_2}\end{matrix} \cdot HCl + ArSO_2Cl + 2NaOH \longrightarrow$$

$$RC\begin{matrix}{}^{\nearrow NSO_2Ar}\\ {}_{\searrow NH_2}\end{matrix} + 2NaCl + 2HOH$$

Carrying out the reaction in acetone, Kwartler and Lucas (84) were able to obtain yields of 51–59 per cent when R was alkyl or aryl. Both *mono-* and *bis*-sulfonamidines may be formed, the proportion varying with the amount of the sulfonyl chloride used in excess and with the temperature (99). The two types of products can be separated easily, since only the latter are soluble in alkali.

$$RC\begin{matrix}{}^{\nearrow NH}\\ {}_{\searrow NH_2}\end{matrix} \xrightarrow{2ArSO_2Cl} RC\begin{matrix}{}^{\nearrow NSO_2Ar}\\ {}_{\searrow NHSO_2Ar}\end{matrix} \xrightarrow{NaOH} RC\begin{matrix}{}^{\nearrow NSO_2Ar}\\ {}_{\searrow \underset{|}{N}SO_2Ar}\\ {}_{Na}\end{matrix}$$

Barber and Newberry (8) found that the use of sodium hydroxide gave excellent yields, an acetone solution or suspension being employed; the use of pyridine resulted in poorer yields, probably because the unsubstituted amidines were stronger bases than pyridine.

Since many amidines are easily hydrolyzed, the reaction must be carried out at or below room temperature. The sulfonamidines are not hydrolyzed as easily; thus mild hydrolytic conditions will produce the following change (8, 84):

$$RC\begin{matrix}{}^{\nearrow N\langle\_\rangle NHCOCH_3}\\ {}_{\searrow NH_2}\end{matrix} \xrightarrow[HCl, 20°C.]{C_2H_5OH} RC\begin{matrix}{}^{\nearrow NSO_2\langle\_\rangle NH_2 \cdot HCl}\\ {}_{\searrow NH_2}\end{matrix}$$

But under more drastic treatment, they will react as follows (8):

$$RC\begin{matrix}{}^{\nearrow NSO_2C_6H_5}\\ {}_{\searrow NH_2}\end{matrix} + HOH \longrightarrow RC\overset{O}{\overset{\|}{N}}HSO_2C_6H_2 + NH_3$$

It has been mentioned previously that tautomerism is possible in the sulfonamidine series. Thus Barber (8) was able to isolate the two isomeric forms XVII and XVIII.

$$RC\!\!\nearrow^{NSO_2R}_{\searrow NH_2} \qquad\qquad RC\!\!\nearrow^{NHSO_2R}_{\searrow NH}$$

$$XVII \qquad\qquad XVIII$$

From a study of the products of hydrolysis, XVIII appeared to be the more stable form. However, Northey, Pierce, and Kertesz (99), concluded that the sulfonamidines could be represented better by XVII, since their compounds did not form alkali salts and because of the nature of the products obtained from hydrolytic cleavage.

$$RC\!\!\nearrow^{NSO_2Ar}_{\searrow NH_2} \; + \; HOH \xrightarrow{H^+ \text{ or } OH^-} RCONH_2 \; + \; ArSO_2NH_2$$

Several workers have reported the preparation of acyl derivatives of monosubstituted amidines (90, 172, 176, 100). Substituted benzamidines and acetamidines have been used; aromatic and aliphatic acid chlorides were employed as the acetylating agents. Wheeler, Johnson, and McFarland (176) report the formation of N-phenyl-N-benzoylbenzamidine.

$$\begin{array}{c} NH_2 \\ 2C_6H_5C\!\!=\!\!NC_6H_5 \end{array} + C_6H_5COCl \xrightarrow{\text{ether}} \begin{array}{c} NH_2\cdot HCl \\ | \\ C_6H_5C\!\!=\!\!NC_6H_5 \end{array} + \begin{array}{c} NH \\ \| \\ C_6H_5CNC_6H_5 \\ | \\ COC_6H_5 \end{array}$$

The latter underwent a molecular rearrangement upon standing or upon recrystallization from hot alcohol to form the more stable substance, N-phenyl-N'-benzoylbenzamidine.

$$C_6H_5C\!\!\nearrow^{NH}_{\searrow \underset{COC_6H_5}{NC_6H_5}} \xrightarrow{\text{heat}} C_6H_5C\!\!\nearrow^{NHCOC_6H_5}_{\searrow NC_6H_5}$$

Hydrolysis of the former substance produced benzamide and benzanilide, whereas similar treatment of the latter produced N-benzoylbenzamide. No conclusions could be drawn from the results, since treatment of N-phenylbenzamidine with acetyl chloride produced N-phenyl-N'-acetylbenzamidine and the more stable N-phenyl-N-acetylbenzamidine.

Walther and Grossmann (172) and the above authors (176) observed that diacyl derivatives are obtained when the reaction is carried out in the presence of pyridine.

$$RC\underset{NH_2}{\overset{NR''}{\big<}} + 2R'COCl + 2C_5H_5N \longrightarrow RC\underset{NCOR'}{\overset{\overset{\displaystyle COR'}{\underset{\displaystyle |}{NR''}}}{\big<}} + 2C_5H_5N \cdot HCl$$

Pinner (109, 120) has reported that benzamidine and ethyl chloroformate react to form *N*-carbethoxybenzamidine. Joshi, Khanolkar, and Wheeler (70) used symmetrical disubstituted amidines and reported that the reaction proceeds smoothly when carried out in the presence of sodium bicarbonate at 20°C.

$$C_6H_5C\underset{NHR}{\overset{NR}{\big<}} + ClCO_2C_2H_5 + NaHCO_3 \longrightarrow$$

$$C_6H_5C\underset{\underset{\displaystyle CO_2C_2H_5}{\overset{\displaystyle |}{NR}}}{\overset{NR}{\big<}} + NaCl + CO_2 + H_2O$$

The same carbethoxy derivative was obtained by the following sequence of reactions:

$$C_6H_5C\underset{NHR}{\overset{NR}{\big<}} \xrightarrow{COCl_2} C_6H_5C\underset{\underset{\displaystyle COCl}{\overset{\displaystyle |}{NR}}}{\overset{NR}{\big<}} \xrightarrow{C_2H_5OH} C_6H_5C\underset{\underset{\displaystyle COOC_2H_5}{\overset{\displaystyle |}{NR}}}{\overset{NR}{\big<}}$$

On the other hand, the reaction of benzamidine with phosgene proceeds in accordance with the following equation (109, 120):

$$C_6H_5C\underset{NH_2}{\overset{NH}{\big<}} + COCl_2 \longrightarrow 2HCl + O{=}C\underset{\underset{\displaystyle NH}{\overset{\displaystyle \|}{NHCC_6H_5}}}{\overset{\overset{\displaystyle NH}{\underset{\displaystyle \|}{NHCC_6H_5}}}{\big<}}$$

The product, however, can be decomposed readily by heat to form a triazine derivative.

An interesting reaction is that between benzamidine and *N*-phenylbenzimidyl chloride (87).

10. Reactions with other active halogen compounds

The reaction of picryl chloride and amidines (172) has been discussed in the section on the preparation of unsymmetrical disubstituted amidines.

Both benzal chloride and α,α-dibromoacetophenone react with benzamidine in a like manner (80, 81).

When α-bromo-α,α-dimethylacetophenone is allowed to react with benzamidine in a chloroform solution a substituted amidine is produced (80).

However, when alpha hydrogen atoms are present, a further reaction takes place in the formation of a substituted imidazole (80).

11. The formation of substituted pyrimidines

Perhaps the most important use of amidines in the field of synthetic chemistry is the synthesis of substituted pyrimidines. Unsubstituted amidines can be made to react with β-ketonic esters, α-formyl esters, other compounds containing β-dicarbonyl groupings, malonic esters, α-cyanonitriles, cyanoacetic esters, α,β-unsaturated carbonyl groups, and ethoxymethylene derivatives of the aforementioned classes to form pyrimidines. Thus many pyrimidines have been prepared which contain the following groups as substituents in the ring: hydroxyl, alkyl, aryl, cyano, amino, nitro, phenylazo, bromo, chloro, acetyl, carbethoxy, and carbethoxymethyl. In one case a benzopyrimidine was prepared, and several substituted dihydropyrimidines have been reported in the literature.

The reactions are usually carried out by allowing the reactants to stand at room temperature in the presence of an alkali hydroxide, potassium carbonate, or sodium ethoxide and ethanol. When compounds containing an α,β-unsaturated carbonyl group are used, the mixture is often heated to effect the reaction.

(a) From β-ketonic esters: According to Pinner (109, 114) the reaction between a β-ketonic ester and an amidine takes place as follows:

The intermediate (XIX) is often isolated as a by-product. Thus 2,6-dimethyl-4-hydroxypyrimidine can be prepared by the reaction of acetamidine and ethyl acetoacetate.

Pinner (109) has stated that formamidine will not form a pyrimidine under the same conditions; otherwise R may be either alkyl or aryl.

The wide applicability of this method can be seen by an inspection of table 2.

Pinner (123) attempted to carry out the same type of reaction with ethyl salicylate, because of its similarity to acetoacetic ester, but the product isolated

TABLE 2

R'	R''	REFERENCES
—CH$_3$	—H	(52, 109, 114)
—COOC$_2$H$_5$	—H	(116)
—H	—H	(53)
—CH$_2$COOC$_2$H$_5$	—H	(127)
—CH$_3$	—CH$_2$COOC$_2$H$_5$	(117)
—CH$_3$	*—CHCOOC$_2$H$_5$ | COCH$_3$	(117)
—CH$_3$	*—COOC$_2$H$_5$	(109, 117, 118)

* The pyrimidines isolated in these cases did not contain the expected carbethoxy group; this is not surprising, since it is known that β-ketonic esters are easily cleaved by alkali, e.g.:

was not a pyrimidine. However, with carbethoxyphloroglucinol, a substituted benzopyrimidine was obtained.

An interesting extension of the reaction is that employing a cyclic β-ketonic ester, 2,5-dicarbethoxy-1,4-cyclohexadione. Two products are obtained according to the following reactions (117):

$$2H_2O + 2C_2H_5OH +$$

$$XX + XXI \qquad CO_2 + 2C_2H_5OH +$$

(b) *From β-dicarbonyl groupings:* Pinner (126) and others (52) have prepared 2-phenyl-4,6-dimethylpyrimidine by the action of benzamidine on acetylacetone in the presence of bases.

4,6-Dimethylpyrimidine is the end product when formamidine hydrochloride is used (52).

Pinner caused benzamidine to condense with the sodio derivative of formylacetone, prepared by treating acetone and ethyl formate with sodium ethoxide, to form a disubstituted pyrimidine.

Hale and Brill prepared 2-phenyl-5-nitropyrimidine in a similar manner (57).

The first step in one of many syntheses of thiamin involves the condensation of acetamidine with the sodium derivative of ethyl α-formyl-β-ethoxypropionate to produce 2-methyl-4-hydroxy-5-ethoxymethylpyrimidine (137). Another

variation uses the condensation of the amidine with ethyl formylsuccinate (2, 66).

$$
\underset{\underset{CH_3CNH_2}{\overset{\parallel}{\text{NH}}}}{} + \underset{C_2H_5OCH_2CCOOC_2H_5}{\overset{\overset{\text{CHONa}}{\parallel}}{}} \longrightarrow \underset{CH_3}{}\begin{array}{c} \text{CH}_2\text{OC}_2\text{H}_5 \\ \text{OH} \end{array}
$$

$$
\underset{\underset{CH_3CNH_2}{\overset{\parallel}{\text{NH}}}}{} + \begin{array}{c} \overset{\text{CHO}}{\text{CHCOOC}_2\text{H}_5} \\ | \\ \text{CH}_2\text{COOC}_2\text{H}_5 \end{array} - \underset{CH_3}{}\begin{array}{c} \text{CH}_2\text{COOC}_2\text{H}_5 \\ \text{OH} \end{array}
$$

(c) *From malonic esters:* Pinner (113, 133) obtained a 50 per cent yield of 2-phenyl-4,6-dihydroxypyrimidine by working up a mixture of benzamidine, diethyl malonate, and sodium ethoxide which had been kept at room temperature for 2 days. When potassium hydroxide was used as the condensing agent, the yield was lowered to 10 per cent.

$$
\underset{\underset{\text{NH}_2}{}}{\overset{\overset{\text{NH}}{\parallel}}{C_6H_5C}} + CH_2(COOC_2H_5)_2 \longrightarrow \underset{C_6H_5}{}\begin{array}{c} \text{OH} \\ \text{OH} \end{array} + 2C_2H_5OH
$$

Kenner *et al.* (82) have shown that formamidine and other aryl and aliphatic amidines react in a similar fashion. Ruhemann (143) has used diethyl chloro- and bromo-malonates to form the 5-chloro- and 5-bromo-pyrimidines.

Dox and Yoder (42) have proposed this reaction as a test for the detection of monoalkylated malonic esters in the presence of dialkylated derivatives.

$$
\underset{\underset{\text{NH}_2}{}}{\overset{\overset{\text{NH}}{\parallel}}{R'-C}} + \begin{array}{c} \text{COOC}_2\text{H}_5 \\ | \\ R-C-H \\ | \\ \text{COOC}_2\text{H}_5 \end{array} \xrightarrow[(70°C.)]{Na} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array} + 2C_2H_5OH
$$

$$
\underset{\underset{\text{NH}_2}{}}{\overset{\overset{\text{NH}}{\parallel}}{R'-C}} + \begin{array}{c} \text{COOC}_2\text{H}_5 \\ | \\ R-C-R \\ | \\ \text{COOC}_2\text{H}_5 \end{array} \xrightarrow[(70°C.)]{Na} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array} + 2C_2H_5OH
$$

The substituted pyrimidones derived from the dialkylated malonic esters are colorless and soluble in neutral solvents; those derived from the monoalkylated derivatives are yellow-orange and insoluble. The authors suggest that the color is due to the enolic structure which is possible only in those compounds derived from the monoalkylated malonic esters.

$$
\begin{array}{ccc}
\underset{\text{(colored)}}{}
\end{array}
$$

(colored)

(d) *From cyano esters:* In 1904 Traube and Herrmann (162) demonstrated that both acetamidine and benzamidine react with ethyl cyanoacetate in the presence of sodium ethoxide to form substituted aminopyrimidines.

$$ RC\!\!\stackrel{NH}{\diagdown NH_2} + CH_2(COOC_2H_5)(CN) \xrightarrow{NaOC_2H_5} C_2H_5OH + \left[RC\!\!\stackrel{NH}{=}\!\!\stackrel{CH_2(CN)}{CO}\!\!-N(H) \right] $$

$$ \left[RC\!\!\stackrel{NH}{=}\!\!\stackrel{CH_2(CN)}{CO}\!\!-N(H) \right] \longrightarrow RC\!\!\stackrel{NH}{=}\!\!\stackrel{CH_2}{CO}\!\!-N(H) \rightleftharpoons RC\!\!\stackrel{NH_2}{=}\!\!\stackrel{CH}{COH}\!\!-N $$

Further studies on this reaction showed that formamidine hydrochloride does not react to produce a cyclic compound, but instead gives good yields of the following product (71):

$$ HC\!\!\stackrel{NH}{\diagdown NH_2} + CH_2(COOC_2H_5)(CN) \xrightarrow{NaOC_2H_5} HC\!\!=\!\!C\!\!\stackrel{NH_2}{\diagup CN}\!\!\stackrel{}{\diagdown COOC_2H_5} + NH_3 $$

In the absence of sodium ethoxide, benzamidine will react to form two products.

$$2C_6H_5C\underset{NH_2}{\overset{NH}{\diagup}} \xrightarrow{CH_2CNCOOC_2H_5} \quad \underset{C_6H_L}{\overset{NH_2}{N}}\underset{N}{\diagup}OH \; + \; C_6H_5C=C\underset{COOC_2H_5}{\overset{CN}{\diagup}}$$

But in the presence of sodium ethoxide, the pyrimidine is the main product.

Ethyl cyanosuccinate condenses with acetamidine hydrochloride to produce the ethyl ester of 2-methyl-4-amino-6-hydroxypyrimidine-5-acetic acid (67), which is a possible intermediate in a synthesis of thiamin. A related condensation is the combination of acetamidine with ethyl α-cyano-β-ethoxypropionate to produce 2-methyl-4-amino-5-carbethoxypyrimidine (73).

$$CH_3\overset{\cdot\cdot}{C}\underset{NH_2}{\overset{NH\cdot HCl}{\diagup}} \; + \; \underset{CH_2COOC_2H_5}{\overset{NC-CHCOOC_2H_5}{|}} \longrightarrow \underset{CH_3}{\overset{NH:}{N}}\underset{N}{\diagup}\overset{CH_2COOC_2H_5}{OH}$$

(e) *From malononitrile*: Amidines also react with malononitrile in the presence of sodium ethoxide to form pyrimidines (5, 71).

$$2RC\underset{NH}{\overset{NH_2}{\diagup}} \; + \; H_2C\underset{CN}{\overset{CN}{\diagup}} \xrightarrow{NaOC_2H_5} \underset{R-C}{\overset{R}{N}}\underset{N}{\overset{C-CN}{C-NH_2}} \; + \; 2NH_3$$

In the case when formamidine was used, the yield was 45 per cent. Both aromatic and aliphatic amidines yield the pyrimidine; however when furamidine was used, the following reaction took place:

$$\begin{array}{c} HC\!-\!CH \\ \| \quad \| \\ HC \quad C\!-\!C \\ \diagdown_O \diagup \diagdown_{NH_2} \end{array}\overset{NH}{\diagup} \; + \; H_2C\underset{CN}{\overset{CN}{\diagup}} \longrightarrow \begin{array}{c} HC\!-\!CH \\ \| \quad \| \\ HC \quad C\!-\!C \\ \diagdown_O \diagup \diagdown_{NH_2} \end{array}\underset{CN}{\overset{CN}{C}} \; + \; NH_3$$

α-Phenylazomalononitrile has also been used to form a substituted pyrimidine.

$$HC\underset{NH_2}{\overset{\cdot NH}{\diagup}} \; + \; \underset{CN}{\overset{CN}{\underset{|}{CHN=NC_6H_5}}} \longrightarrow \underset{N}{\overset{NH_2}{N}}\underset{N}{\overset{N=NC_6H_5}{NH_2}}$$

(f) *From unsaturated carbonyl compounds:* In 1897 Ruhemann (142) reported the preparation of a phenylcarbethoxypyrimidine from benzamidine and diethyl 1,3-dicarbethoxyglutaconate by heating the two at 100°C. in the presence of sodium and ethyl alcohol.

$$C_6H_5C\begin{array}{c}NH\\ \\NH_2\end{array} + \begin{array}{c}C(COOC_2H_5)_2\\ \|\\CH\\ \backslash\\CH(COOC_2H_5)_2\end{array} \longrightarrow \begin{array}{c}CH\\HN \diagup \diagdown CCOOC_2H_5\\ | \quad\quad |\\C_6H_5C \quad C=O\\ \diagdown \diagup\\N\end{array}$$

Traube and Schwarz (163) have attempted to carry out the above type of reaction using unsaturated ketones and aldehydes such as benzalacetone, acrolein, and cinnamaldehyde. Although these compounds reacted vigorously, no crystalline products could be isolated. When mesityl oxide and phorone were used, analytically pure products could be isolated.

$$2C_6H_5C\begin{array}{c}NH\\ \diagup\\ \diagdown\\NH_2\end{array} + (CH_3)_2C{=}CHCOCH{=}C(CH_3)_2 \longrightarrow$$

$$\begin{array}{c}(CH_3)_2CCH_2COCH_2C(CH_3)_2\\ | \quad\quad\quad\quad |\\NH \quad\quad\quad NH\\ | \quad\quad\quad\quad |\\C_6H_5C{=}NH \quad HN{=}CC_6H_5\end{array}$$
XXII

Further heating of the triacetone dibenzamidine produced a substituted dihydropyrimidine.

$$XXII \longrightarrow \begin{array}{c}CH_3\\ |\\CH_2CNHCOC_6H_5\\ | \quad |\\C \quad CH_3\\ \diagup \diagdown\\N \quad\quad CH\\ \| \quad\quad | \diagup CH_3\\C_6H_5{-}C \quad C \diagdown CH_3\\ \\ \dot{H}\end{array} + NH_3$$

A similar equation can be written for the reaction between benzamidine and mesityl oxide; the product formed is substituted in the 6-position by a methyl group.

By allowing benzamidine and ethyl phenylpropiolate to react in the presence of sodium ethoxide at 100°C., a diphenylpyrimidine is formed (147).

$$C_6H_5C\begin{matrix}NH_2\\\\NH\end{matrix} + \begin{matrix}C_2H_5OCO\\C\\\parallel\\C-C_6H_5\end{matrix} \rightarrow \begin{matrix}HN-C(=O)-CH\\ \mid \qquad \parallel \\ C_6H_5-C \qquad C-C_6H_5\\ \diagdown N \diagup \end{matrix} + C_2H_5OH$$

If the reaction is carried out at 20°C., a compound containing a five-membered ring is formed. According to Ruhemann and Cunnington, the compound has one of the following structures (146):

$$\begin{matrix}HN-C=O\\ \mid \quad \mid \\ C_6H_5C \quad C=CHC_6H_5 \\ \diagdown N \diagup \end{matrix} \quad \text{or} \quad \begin{matrix}N-C=O\\ \parallel \quad \mid \\ C_6H_5C \quad C=CHC_6H_5 \\ \diagdown N \diagup \\ H \end{matrix}$$

Ruhemann has studied the reaction of various compounds containing α,β-unsaturated carbonyl groupings (143, 144, 145) with benzamidine; in each case a substituted pyrimidine was formed: diethyl benzalmalonate, ethyl benzalacetoacetate, benzylideneacetylacetone, etc. were used.

Various mechanisms have been proposed for the formation of the cyclic compounds from the reaction of an amidine with an unsaturated carbonyl compound, but none of them have been proven. It is interesting to observe that the formation of the pyrimidine derivatives mentioned in these references could be explained by a mechanism involving a 1,4-addition, commonly associated with compounds containing an α,β-unsaturated carbonyl group.

Mittler et al. (96) have studied the condensation of amidines with ethoxymethylene derivatives of β-ketonic esters, β-diketones, and cyanoacetic ester and found that substituted pyrimidines were produced. The following equations represent the extent of the work:

$$ArC\begin{matrix}NH\\ \\ NH_2\end{matrix} + C_2H_5OCH{=}\overset{R}{\underset{}{C}}COCH_3 \xrightarrow[C_2H_5OH]{NaOC_2H_5}$$

$$\begin{matrix} & CH \\ & \diagup \quad \diagdown \\ N & \quad CR \\ \parallel & \quad \mid \\ ArC & \quad CCH_3 \\ & \diagdown \quad \diagup \\ & N \end{matrix} + C_2H_5OH + H_2O$$

$R = -COCH_3 \quad \text{or} \quad -CO_2C_2H_5$

$$ArC\overset{NH}{\underset{NH_2}{<}} + \overset{COOC_2H_5}{\underset{COOC_2H_5}{C=CHOC_2H_5}} \rightarrow \begin{array}{c} CH \\ HN\diagup\diagdown CCOOC_2H_5 \\ ArC \quad C=O \\ \diagdown N\diagup \end{array} + 2C_2H_5OH$$

$$ArC\overset{NH_2}{\underset{NH}{<}} + C_2H_5OCH=CCOOC_2H_5 \rightarrow \begin{array}{c} CH \\ HN\diagup\diagdown CCN \\ ArC \quad C=O \\ \diagdown N\diagup \end{array} + 2C_2H_5OH$$

(the second reactant bears CN below: $\underset{CN}{C_2H_5OCH=CCOOC_2H_5}$)

(g) *Miscellaneous:* Pinner obtained 2-phenyl-3,4,5,6-tetrahydropyrimidine by the alkylation of benzamidine with trimethylene bromide (126).

$$C_6H_5C\overset{NH}{\underset{NH_2}{<}} + BrCH_2CH_2CH_2Br \rightarrow \begin{array}{c} CH_2 \\ N\diagup\diagdown CH_2 \\ C_6H_5C \quad CH_2 \\ \diagdown NH\diagup \end{array} + 2HBr$$

Pinner also reported the formation of 2,4-dimethyl-6-acetylaminopyrimidine by the thermal decomposition of acetamidine in the presence of sodium acetate and acetic anhydride (115).

Kunckell and Sarfert (83) utilized a β-bromoketone in synthesizing a dihydropyrimidine.

$$C_6H_5C\overset{NH}{\underset{NH_2}{<}} + \begin{array}{c} C_6H_5 \\ CO \\ CH_2 \\ CHC_6H_5 \\ Br \end{array} \xrightarrow{CHCl_3} \begin{array}{c} C_6H_5 \\ C \\ N\diagup\diagdown CH \\ C_6H_5C \quad CHC_6H_5 \\ \diagdown NH\diagup \end{array} + H_2O + HBr$$

Kunckell and Zumbusch (82) reported the following reaction:

$$C_6H_5C\overset{NH}{\underset{NH_2}{<}} + \overset{Br\;Br}{\underset{CHO}{C=CCOOH}} \xrightarrow{CHCl_3} \begin{array}{c} COOH \\ C \\ N\diagup\diagdown C-Br \\ C_6H_5-C \quad CH \\ \diagdown N\diagup \end{array} + HBr + H_2O$$

12. Formation of imidazoles and imidazolones

Kunckell has obtained an imidazole by treating an amidine with α-bromo-acetophenone (80), and Ruhemann and Cunnington (146) demonstrated the formation of benzalimidazolone from the action of ethyl phenylpropiolate on benzamidine. Ekeley has studied the reaction between 1,2-dicarbonyl compounds and amidines (45, 46, 47, 173). Thus, when benzamidine hydrochloride and phenylglyoxal hydrate are caused to react in the cold and in the presence of an excess of base (potassium hydroxide), an addition product (XXIII) is formed (173). When the basic solution of this addition compound is heated, a cyclization occurs with the formation of an imidazolone (XXIV). When either compound XXIII or compound XXIV is treated with an excess of hydrochloric acid, a third compound (XXV) is formed which is very unstable in the absence of acids. These relationships are indicated by the following equations:

$$
\underset{NH_2}{\overset{NH}{C_6H_5C}} \cdot HCl \; + \; C_6H_5\overset{O}{\overset{\|}{C}}CH(OH)_2 \xrightarrow[C_2H_5OH]{\text{excess KOH}}
$$

$$
\underset{XXIV}{\underset{\underset{C_6H_5}{|}}{\underset{C}{\overset{C_6H_5C=\!=\!=COH}{\underset{N\quad\quad NH}{\diagdown\;\;\diagup}}}}}
\quad or \quad
\underset{\underset{C_6H_5}{|}}{\underset{C}{\overset{C_6H_5CH\!-\!-\!-C=O}{\underset{N\quad\quad NH}{\diagdown\;\;\diagup}}}}
\xleftarrow[-H_2O]{heat}
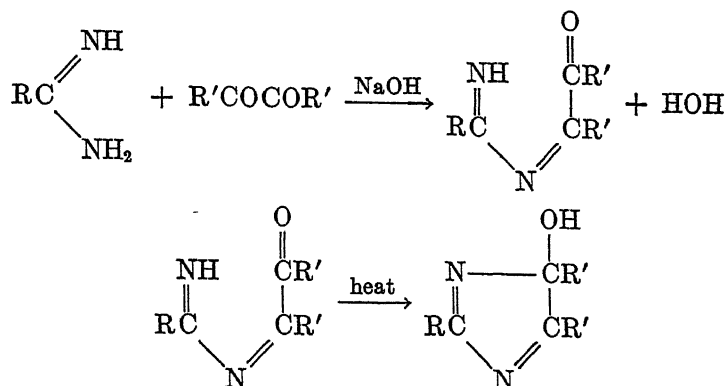\underset{XXIII}{\overset{NH\;\;OH\;\;O}{C_6H_5\overset{\|}{C}NH\overset{|}{C}H\!-\!\overset{\|}{C}C_6H_5}}
$$

$$
\underset{XXV}{\underset{\underset{C_6H_5}{|}}{\underset{C}{\overset{\overset{OH\quad\quad OH}{C_6H_5\overset{|}{C}\!-\!-\!-\!\overset{|}{C}H}}{\underset{N\quad\quad NH\cdot HCl}{\diagdown\;\;\diagup}}}}}
$$

HCl / +H₂O   +H₂O / HCl
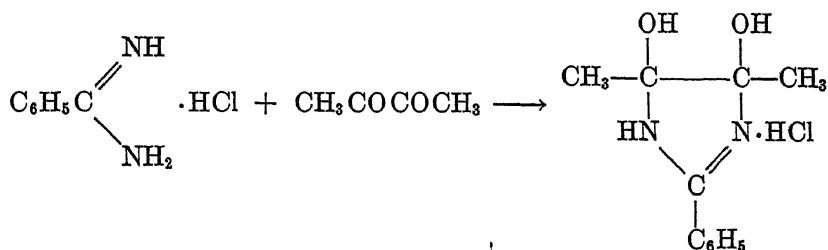
J. O. Cole (31) obtained 70 per cent yields of compound XXIV when aliphatic amidines were used. Cole also reports that a very complex mixture of compounds is obtained when only enough base is used to neutralize the hydrochloride.
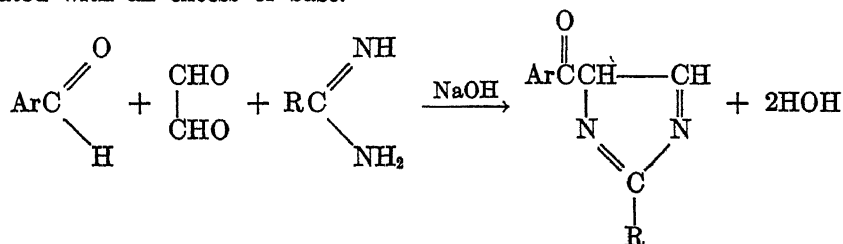
From experiments with aliphatic and aromatic 1,2-diketones Pinner (109) concluded that the following reactions were general for these types of compounds:

$$RC\begin{matrix}NH \\ \\ NH_2\end{matrix} + R'COCOR' \xrightarrow{NaOH} RC\begin{matrix}NH & CR'(=O) \\ \\ & CR' \\ N \end{matrix} + HOH$$

$$RC\begin{matrix}NH & CR'(=O) \\ \\ & CR' \\ N \end{matrix} \xrightarrow{heat} RC\begin{matrix}N—CR'(OH) \\ \\ CR' \\ N \end{matrix}$$

Diels and Schleich (40) concluded that the following reaction between benzamidine hydrochloride and diacetyl probably takes place:

$$C_6H_5C\begin{matrix}NH \\ \\ NH_2\end{matrix} \cdot HCl + CH_3COCOCH_3 \longrightarrow \begin{matrix}OH & OH \\ CH_3—C—————C—CH_3 \\ HN & N\cdot HCl \\ & C \\ & C_6H_5\end{matrix}$$

Ekeley, Ronzio, and Elliott (45, 46, 47) observed that a definite reaction takes place when a mixture of an aromatic aldehyde, glyoxal, and an amidine are treated with an excess of base.

$$ArC\begin{matrix}O \\ \\ H\end{matrix} + \begin{matrix}CHO \\ | \\ CHO\end{matrix} + RC\begin{matrix}NH \\ \\ NH_2\end{matrix} \xrightarrow{NaOH} \begin{matrix}O \\ ArCCH————CH \\ N & N \\ & C \\ & R\end{matrix} + 2HOH$$

In 1901 Kunckell and Bauer (81) reported that phenylglyoxal forms a condensation product with benzamidine. This product melted at nearly the same temperature as cyaphenine and may possibly be the latter (173).

Kulisch (79) has prepared 2,4,5-triphenylimidazole ("*Lophin*") by heating benzamidine hydrochloride and benzoin in the presence of ethanol and an excess of sodium hydroxide.

$$C_6H_5C\begin{matrix}NH \\ \\ NH_2\end{matrix} + C_6H_5COCHC_6H_5(OH) \longrightarrow \begin{matrix}C_6H_5C————N \\ C_6H_5C & CC_6H_5 \\ & NH\end{matrix} + 2H_2O$$

13. Formation of triazines

2-Methyl-4,6-diamino-1,3,5-triazine has been prepared in a 65 per cent yield by heating a mixture of acetamidine hydrochloride and cyanoguanidine at 230°C. (102).

$$\text{CH}_3\text{C}\!\!\overset{\text{NH}}{\underset{\text{NH}_2}{\big|}}\!\! \cdot \text{HCl} + \text{H}_2\text{N}\overset{\text{NH}}{\text{C}}\text{NHCN} \longrightarrow \quad + \text{NH}_4\text{Cl}$$

The corresponding phenyl-substituted compound is obtained by employing benzamidine hydrochloride. Closely related to the above reactions is the formation of a substituted triazine when diphenylformamidine is heated with phenylbiguanide (164).

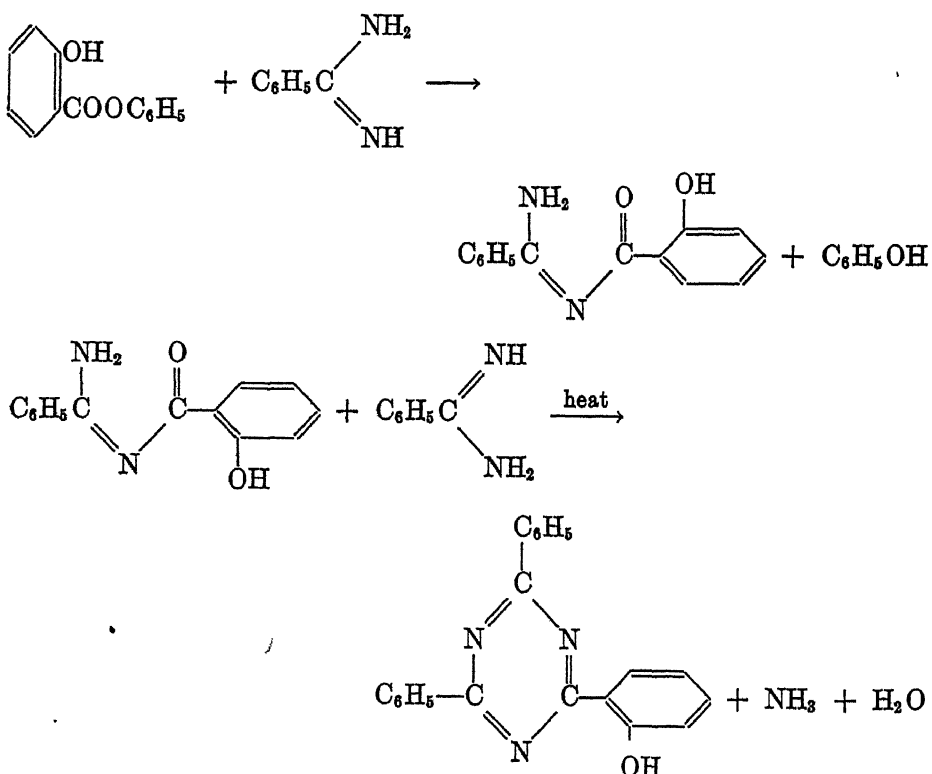Titherley and Hughes (160) obtained 2,4-diphenyl-6-o-hydroxyphenyl-1,3,5-triazine by heating with benzamidine the condensation product obtained by the action of this same amidine on phenyl salicylate.

$$\text{(structures)} + \text{C}_6\text{H}_5\text{C}\!\!\overset{\text{NH}_2}{\underset{\text{NH}}{\big|}}\!\! \longrightarrow$$

$$\longrightarrow \quad + \text{C}_6\text{H}_5\text{OH}$$

$$\text{(structure)} + \text{C}_6\text{H}_5\text{C}\!\!\overset{\text{NH}}{\underset{\text{NH}_2}{\big|}}\!\! \xrightarrow{\text{heat}}$$

$$\longrightarrow \quad + \text{NH}_3 + \text{H}_2\text{O}$$

Pinner had previously reported the isolation of this triazine from the many products obtained from the reaction between benzamidine and the ethyl ester of salicylic acid (124). Carbethoxyphloroglucinol, however, reacts to form a benzopyrimidine (123).

Pinner also found that the treatment of benzamidine with acetic anhydride produces 2-methyl-4,6-diphenyl-1,3,5-triazine (125, 130). The following mechanism for this transformation was suggested (109):

Pinner obtained a triazine by the action of phosgene or ethyl chloroformate on benzamidine (120). As pointed out previously, these reagents react with benzamidine to form non-cyclic intermediates first which can be isolated. The triazines can then be formed by heating the intermediates.

$$C_6H_5C \overset{NH}{\underset{NH_2}{\Big\langle}} \xrightarrow{COCl_2} (C_6H_5\overset{NH}{\overset{\|}{C}}NH)_2CO \xrightarrow{\text{heat}}$$

$$\xrightarrow{ClCOOC_2H_5} 2\,C_6H_5C \overset{NH}{\underset{NHCOOC_2H_5}{\Big\langle}} \xrightarrow{\text{heat}}$$

The same triazine is formed when the compound obtained from the reaction of diethyl acetylmalonate and benzamidine in the presence of potassium carbonate is heated to 200°C. (118).

$$C_6H_5C\overset{NH}{\underset{NH_2}{\Big\langle}} + CH_3CO\overset{COOC_2H_5}{\underset{COOC_2H_5}{\overset{|}{C}H}} \xrightarrow[\text{2HOH}]{K_2CO_3} \downarrow$$

$$CH_3CO\overset{CONH\overset{NH}{\overset{\|}{C}}C_6H_5}{\underset{COOH \cdot C_6H_5C\overset{NH}{\underset{NH_2}{\Big\langle}}}{\overset{|}{C}H}} + 2C_2H_5OH$$

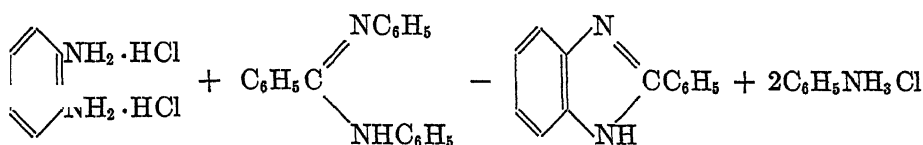$$\xleftarrow{\text{heat}} (C_6H_5\overset{NH}{\overset{\|}{C}}NH)_2CO + CO_2 + CH_3COCH_3$$

The formation of the triazine in this case seems unusual, since β-ketonic esters usually react with amidines to form pyrimidines. By using sodium hydroxide instead of the potassium carbonate, Pinner did obtain the expected pyrimidine (109, 117, 118).
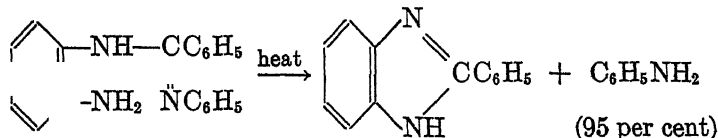
14. Formation of miscellaneous heterocycles from amidines

Benzimidazoles may be prepared by fusing amidines, acids, esters or nitriles with o-phenylenediamine. According to Wagner (61, 164) the yield is seldom improved by the use of amidines.

Hölljes and Wagner (61) obtained 2-phenylbenzimidazole by heating o-phenylenediamine hydrochloride and an excess of N,N'-diphenylbenzamidine at 200°C.

No reaction took place when the free base was used; Wagner (164) obtained a yield of 64 per cent of the 2-methyl derivative when the corresponding acetamidine was used. N-Phenyl-N'-o-aminophenylbenzamidine or its hydrochloride yields 2-phenylbenzimidazole upon heating to 200°C. (61).

Benzimidazole itself may be prepared in 81 per cent yield by heating diarylformamidines with o-phenylenediamine (164).

Hölljes and Wagner also prepared 2-phenylbenzoxazole in 94 per cent yield by heating N-phenyl-N'-o-hydroxyphenylbenzamidine at 100°C.

The reactions between o-aminophenol and N,N'-diphenylacetamidine likewise produced the 2-methyloxazole (164).

Wagner (164) prepared perimidine in 81 per cent yield by heating 1,8-diaminonaphthalene and N,N'-diphenylformamidine.

When *o*-aminobenzylphenylamine was heated with diarylformamidines, a dihydroquinazoline was formed in fair yields.

This method was not successful when acetamidine was employed.

Various modifications of the Niementowski reaction employing the use of amidines in the synthesis of 4-keto-3,4-dihydroquinazolines have been reported (95, 164).

$(R = H, Ar)$

No reaction product could be isolated when acetamidine was employed. Anthranilic acid or its methyl ester may also be used (95).

R may be H or CH_3. Yields as high as 90 per cent were obtained when isatoic anhydride was substituted for the anthranilic acid.

Titherley and Hughes (158, 159) have isolated benzoxazones from the reaction mixture obtained by heating N-phenylbenzamidine and substituted salicylic esters. The following equations indicate the proposed mechanism for the production of 2-phenyl-1,3-benzoxazine-4-one:

15. Reaction of amidines with aldehydes

Pinner (109, 115, 121) and Kunckell and Bauer (81) have shown that the following reaction of amidines is general:

$$RC\!\!\underset{NH_2}{\overset{NH}{}} + R'CHO \longrightarrow RC\!\!\underset{N=CHR'}{\overset{NH}{}} + HOH$$

Thus, by refluxing a chloroform solution of benzamidine and an excess of benzaldehyde, N-benzalbenzamidine is formed (81). However, Pinner (121) observed the formation of many side products in this reaction. Freshly distilled acetaldehyde reacts in the following manner:

$$3CH_3CHO + C_6H_5C\overset{NH}{\underset{NH_2}{\diagup}} \rightarrow C_6H_5C\overset{NH}{\underset{}{N}}\overset{CH_3}{\underset{CH-O}{\overset{|}{CH-O}}}\overset{}{\underset{}{CHCH_3}} + HOH$$

When the product of the reaction between benzamidine and formaldehyde is treated with hot water, bis(benzoylamino)methane is produced.

$$2C_6H_5C\overset{NH}{\underset{NH_2}{\diagup}} + HCHO \rightarrow CH_2(NH\overset{NH}{\overset{\|}{C}}C_6H_5)_2 \xrightarrow{HOH} CH_2(NH\overset{O}{\overset{\|}{C}}C_6H_5)_2$$

16. Reaction of formamidines with active methylene compounds

F. B. Dains has published ten papers on the reaction of symmetrical disubstituted formamidines with compounds containing active methylene groups (34, 35, 36, 37). The conclusions drawn from his work can be represented by the following equation:

$$HC\overset{NR}{\underset{NHR}{\diagup}} + \overset{X}{\underset{CH_2}{\diagdown\diagup}}\overset{Y}{} \xrightarrow{heat} HC\overset{NHR}{\underset{C-X}{\diagdown}}\underset{\overset{|}{Y}}{} + RNH_2$$

R may be alkyl or aryl, and X and Y are radicals which activate the methylene group. Those compounds which contain this type of methylene group include ethyl acetoacetate, acetylacetone, diethyl malonate, acetoacetanilide, and ethyl cyanoacetate.

When X or Y is a carbethoxy radical, a further reaction takes place.

$$HC\overset{NHR}{\underset{CCOOC_2H_5}{\diagup}}\underset{\overset{|}{X}}{} + RNH_2 \xrightarrow{heat} HC\overset{NHR}{\underset{CCONHR}{\diagup}}\underset{\overset{|}{X}}{} + C_2H_5OH$$

Thus with diethyl malonate, the amide is formed in yields as high as 80 per cent; however, the reaction with ethyl cyanoacetate does not produce the amide. Benzyl cyanide and benzyl phenyl ketone react with difficulty (34).

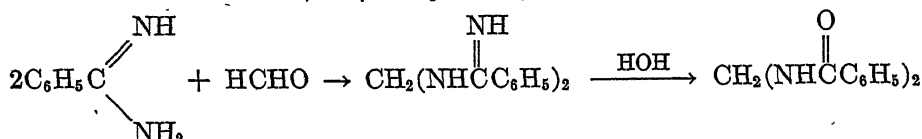The reaction between the substituted formamidines and active methylene compound is carried out by heating the two at 125–200°C. for several hours.

Cyclic compounds containing an active methylene group can be used as well. The reactions of a number of 1,3-disubstituted pyrazolones have been studied. Thus, 1-phenyl-3-methyl-5-pyrazolone reacts as follows:

$$\underset{\substack{| \\ C_6H_5}}{CH_3C\text{---}CH_2} + HC\underset{NR}{\overset{NHR}{\Big|}} \rightarrow \underset{\substack{| \\ C_6H_5}}{CH_3\text{--}C\text{---}C=CHNHR} + RNH_2$$

The products, alkylaminomethenyl derivatives, are all colored. When the pyrazolone is used in excess the following reaction takes place:

$$2\ \underset{\substack{| \\ C_6H_5}}{CH_3C\text{---}CH_2} + HC\underset{NR}{\overset{NHR}{\Big|}} \rightarrow \underset{\substack{| \\ C_6H_5}}{CH_3C\text{---}C=CH\text{---}CH\text{---}CCH_3} + 2RNH_2$$

Isoxazolines and thioimidazolones react with these formamidines in the usual manner.

$$\underset{O}{R'C\text{---}CH_2} + HC\underset{NHR}{\overset{NR}{\Big|}} \xrightarrow{\text{heat}} R'C\text{---}C=CHNHR + RNH_2$$

$$\underset{\substack{| \\ \dot{R}'}}{R'N\text{---}C=O} + HC\underset{NHR}{\overset{NR}{\Big|}} \xrightarrow{\text{heat}} R'N\text{---}C=O + RNH_2$$

An interesting reaction takes place when 3-methyl-4-benzal-5-isoxazolone is treated with N,N'-diphenylformamidine.

$$\underset{O}{CH_3C\text{---}C=CHC_6H_5} + HC\underset{NHC_6H_5}{\overset{NC_6H_5}{\Big|}} \xrightarrow{\text{heat}}$$

$$CH_3C\text{---}C=CHNHC_6H_5 + C_6H_5CH=NC_6H_5$$

Dains has extended the work to show that all 4-thiazolidones react in the same manner with substituted formamidines.

$$C_6H_5N\text{---}C{=}O$$
$$\underset{\diagdown S}{C_6H_5N{=}C}\quad CH_2 \quad + \quad HC\overset{NR}{\underset{NHR}{\diagup}}\xrightarrow{\text{heat}}$$

$$C_6H_5N\text{---}C{=}O$$
$$\underset{\diagdown S}{C_6H_5N{=}C}\quad C{=}CHNHR \quad + \quad RNH_2$$

The other types of thiazolones studied had the following general structures:

$$RN\text{---}C{=}O \qquad HN\text{---}C{=}O \qquad N\text{---}C{=}O$$
$$O{=}C\quad CH_2 \qquad S{=}C\quad CH_2 \qquad RSC\quad CH_2$$
$$\diagdown S \qquad\qquad \diagdown S \qquad\qquad \diagdown S$$

$$N\text{---}C{=}O \qquad RN\text{---}C{=}O$$
$$R_2NC\quad CH_2 \qquad RN{=}C\quad CH_2$$
$$\diagdown S \qquad\qquad \diagdown S$$

The reactivity of these compounds to disubstituted formamidines illustrates that the methylene group in the structure

$$\left[\begin{array}{c} O \\ \| \\ \text{---C---CH}_2\text{---S---} \end{array} \right]$$

is active.

17. Reduction of amidines

The degradative reduction of amidines has been used to determine structures when hydrolysis failed or was difficult (9, 135). The procedure most commonly used for the reduction is to dissolve the amidine in absolute ethanol and to heat the solution over a water bath for several hours with sodium amalgam and acetic acid (9, 74, 135).

Thus Pyman (135) was able to reduce N-methyl-N'-benzylbenzamidine, an amidine which could not be hydrolyzed by boiling with 20 per cent sodium hydroxide.

$$C_6H_5C\overset{NCH_3}{\underset{NHCH_2C_6H_5}{\diagup}} \quad + \quad 4[H] \xrightarrow[C_2H_5OH]{Na/Hg} (C_6H_5CH_2)_2NH \quad + \quad CH_3NH_2 \text{ .}$$

Beckmann and Fellrath (9) have reduced a trisubstituted amidine.

$$\text{C}_6\text{H}_5\text{C} \underset{\substack{| \\ \text{CH}_3}}{\overset{\text{NC}_6\text{H}_5}{\underset{\text{NCH}_2\text{C}_6\text{H}_5}{\diagup}}} + 4[\text{H}] \xrightarrow[\text{C}_2\text{H}_5\text{OH}]{\text{Na/Hg}} \text{C}_6\text{H}_5\text{CH}_2\text{NHC}_6\text{H}_5 + \text{CH}_3\text{NHCH}_2\text{C}_6\text{H}_5$$

In 1880 Bernthsen and Szymanski (14) reported the isolation of a reduction product from N-phenylbenzamidine which they termed *dihydrophenylbenzamidine*. Later investigators suggested that the reported dihydro derivative was probably the unchanged amidine (74). Kirsanov and Ivaschchenko further studied the reduction of N-phenylbenzamidine, using sodium amalgam and acetic acid in absolute alcohol (74). Employing an isolation procedure which involved an aqueous acid treatment, they recovered approximately 74 per cent of unchanged amidine as well as smaller amounts of benzaldehyde, aniline, benzylaniline, and benzylamine. To explain the formation of these compounds they proposed the following reactions, which involve an unstable dihydrophenylbenzamidine:

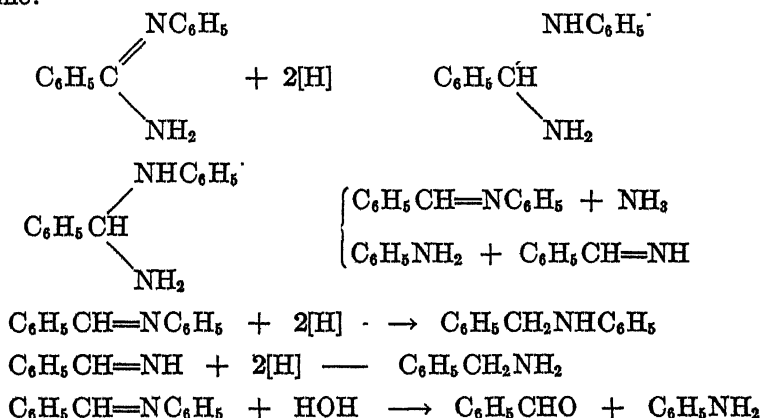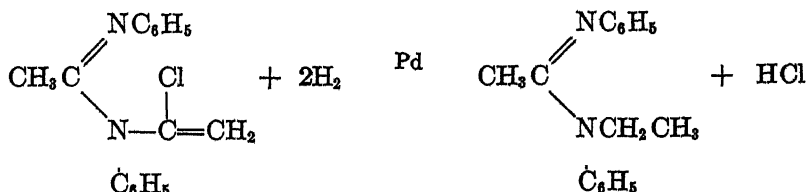$$\text{C}_6\text{H}_5\text{C} \overset{\text{NC}_6\text{H}_5}{\underset{\text{NH}_2}{\diagup}} + 2[\text{H}] \qquad \text{C}_6\text{H}_5\dot{\text{C}}\text{H} \overset{\text{NHC}_6\text{H}_5}{\underset{\text{NH}_2}{\diagdown}}$$

$$\text{C}_6\text{H}_5\dot{\text{C}}\text{H} \overset{\text{NHC}_6\text{H}_5}{\underset{\text{NH}_2}{\diagup}} \quad \begin{cases} \text{C}_6\text{H}_5\text{CH}{=}\text{NC}_6\text{H}_5 + \text{NH}_3 \\ \text{C}_6\text{H}_5\text{NH}_2 + \text{C}_6\text{H}_5\text{CH}{=}\text{NH} \end{cases}$$

$$\text{C}_6\text{H}_5\text{CH}{=}\text{NC}_6\text{H}_5 + 2[\text{H}] \cdot \longrightarrow \text{C}_6\text{H}_5\text{CH}_2\text{NHC}_6\text{H}_5$$

$$\text{C}_6\text{H}_5\text{CH}{=}\text{NH} + 2[\text{H}] \longrightarrow \text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$$

$$\text{C}_6\text{H}_5\text{CH}{=}\text{NC}_6\text{H}_5 + \text{HOH} \longrightarrow \text{C}_6\text{H}_5\text{CHO} + \text{C}_6\text{H}_5\text{NH}_2$$

Houben (62) mentions that an N,N'-diphenyl-substituted amidine may be reduced to an aldehyde; an alcoholic solution of the amidine is refluxed in the presence of sodium, and the reaction mixture is worked up after treatment with dilute hydrochloric acid.

von Braun, Jostes, and Heymons (18) cited an example in which an amidine was not reduced catalytically. Thus, when N-α-chlorovinyl-N, N'-diphenylacetamidine was treated with hydrogen under slight pressure at room temperature in the presence of palladized charcoal and dilute acid, the amidine linkages were not changed but halogen was removed and the vinyl group reduced.

$$\text{CH}_3\text{C} \underset{\underset{\dot{\text{C}}_6\text{H}_5}{\text{N}\text{---}\text{C}{=}\text{CH}_2}}{\overset{\text{NC}_6\text{H}_5}{\diagup \diagdown \text{Cl}}} + 2\text{H}_2 \xrightarrow{\text{Pd}} \text{CH}_3\text{C} \underset{\underset{\dot{\text{C}}_6\text{H}_5}{\text{NCH}_2\text{CH}_3}}{\overset{\text{NC}_6\text{H}_5}{\diagup}} + \text{HCl}$$
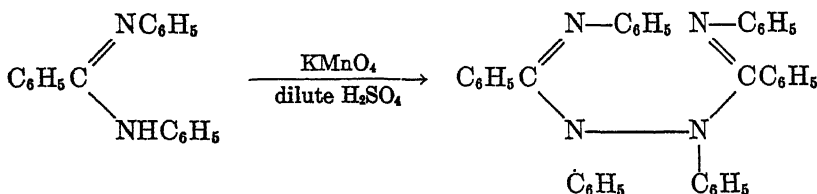
Kubiczek (77), however, claims that the statement of von Braun *et al.* that amidines cannot be hydrogenated by hydrogen and palladized charcoal is not true, at least for all amidines. He treated N,N'-di-*m*-tolylbenzamidine with hydrogen and palladium black at 18°C. as above for 34 hr., and isolated *m*-toluidine and toluene. The hydrogenation is so slow that it may easily be overlooked.

Henle (58) reduced benzamidine hydrochloride to ammonia and benzylamine in a yield of 38 per cent by treating a cooled aqueous solution of the salt with sodium amalgam and hydrochloric acid.

Beckmann and Fellrath (9) studied the reduction of amidines, using zinc dust and acetic acid; some reduction occurred but unchanged amidine was also recovered.
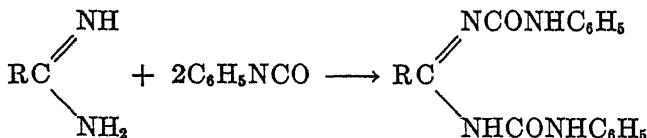
18. Oxidation of amidines

Joshi, Khanolkar, and Wheeler (70) have shown that N,N'-diphenylbenz-amidine may be oxidized with potassium permanganate and dilute sulfuric acid at 100°C. to form *s*-diphenyldi(phenyliminobenzyl)hydrazine. The results were extended to show that the reaction is general for diaryl-substituted benzamidines.

$$
\underset{\substack{\\ \text{NHC}_6\text{H}_5}}{\overset{\substack{\text{NC}_6\text{H}_5 \\ }}{\text{C}_6\text{H}_5\text{C}}} \quad \xrightarrow[\text{dilute H}_2\text{SO}_4]{\text{KMnO}_4} \quad
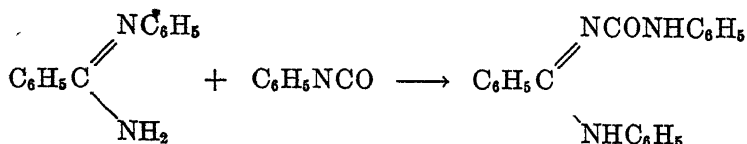$$

19. Formation of substituted ureas

As early as 1889 Pinner (109, 115, 121) demonstrated that both aromatic and aliphatic amidines can easily be made to react with phenyl isocyanate to form the corresponding phenylureides.

$$
\underset{\substack{\\ \text{NH}_2}}{\overset{\substack{\text{NH} \\ }}{\text{RC}}} \quad + \quad 2\text{C}_6\text{H}_5\text{NCO} \quad \longrightarrow \quad
\underset{\substack{\\ \text{NHCONHC}_6\text{H}_5}}{\overset{\substack{\text{NCONHC}_6\text{H}_5 \\ }}{\text{RC}}}
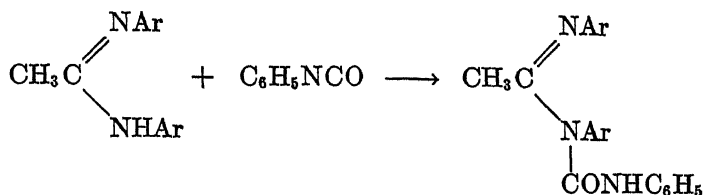$$

A solution of the amidine in anhydrous ether or benzene is treated with a solution of phenyl isocyanate at room temperature. The derivative either separates at once (175) or else the solvent is then removed and the residue crystallized from acetone or alcohol (121).

Wheeler (175) and Walther and Grossmann (172) have prepared the phenylureides of monosubstituted amidines.

$$
\underset{\substack{\\ \text{NH}_2}}{\overset{\substack{\text{NC}_6\text{H}_5 \\ }}{\text{C}_6\text{H}_5\text{C}}} \quad + \quad \text{C}_6\text{H}_5\text{NCO} \quad \longrightarrow \quad
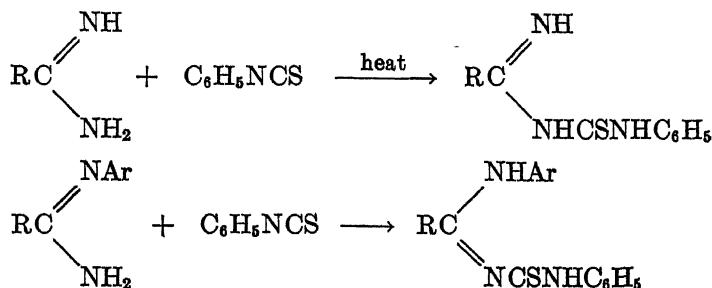\underset{\substack{\\ \text{NHC}_6\text{H}_5}}{\overset{\substack{\text{NCONHC}_6\text{H}_5 \\ }}{\text{C}_6\text{H}_5\text{C}}}
$$

Hill and Rabinowitz (60) have characterized various symmetrical disubstituted amidines by conversion to the corresponding phenylureides.

$$CH_3C\!\!\begin{array}{c}\nearrow NAr\\[6pt]\searrow NHAr\end{array} \quad + \quad C_6H_5NCO \quad\longrightarrow\quad CH_3C\!\!\begin{array}{c}\nearrow NAr\\[6pt]\diagdown \underset{\underset{CONHC_6H_5}{|}}{NAr}\end{array}$$
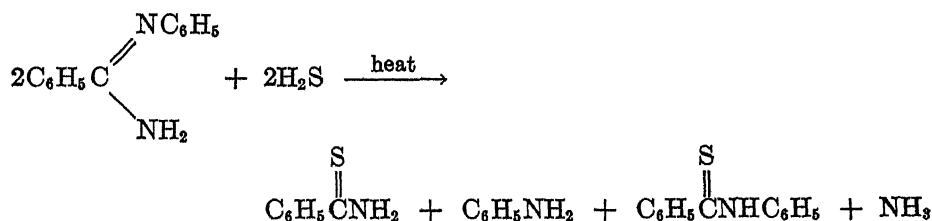
The yields of the derivatives are good, and the melting points are generally not too high.

Pinner (115) and others (172, 175) have also prepared derivatives of amidines by the use of phenyl isothiocyanate.
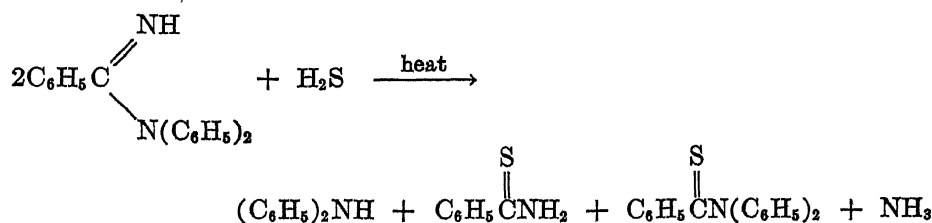
$$RC\!\!\begin{array}{c}\nearrow NH\\[6pt]\searrow NH_2\end{array} \quad + \quad C_6H_5NCS \quad\xrightarrow{\text{heat}}\quad RC\!\!\begin{array}{c}\nearrow NH\\[6pt]\searrow NHCSNHC_6H_5\end{array}$$

$$RC\!\!\begin{array}{c}\nearrow NAr\\[6pt]\searrow NH_2\end{array} \quad + \quad C_6H_5NCS \quad\longrightarrow\quad RC\!\!\begin{array}{c}\diagup NHAr\\[6pt]\diagdown\!\!\diagdown NCSNHC_6H_5\end{array}$$
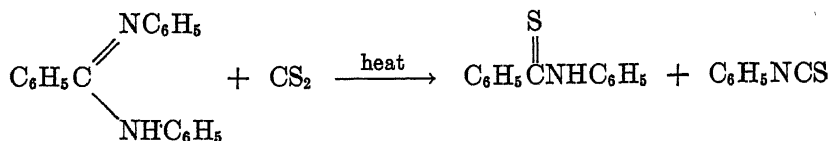
20. Formation of thioamides

Bernthsen has studied the action of hydrogen sulfide and carbon disulfide on various amidines (12). Thioamides were produced in all of the reactions studied. When *N*-phenylbenzamidine was heated to 120°C. in the presence of hydrogen sulfide gas, the following reaction took place:

$$2C_6H_5C\!\!\begin{array}{c}\nearrow NC_6H_5\\[6pt]\searrow NH_2\end{array} \quad + \quad 2H_2S \quad\xrightarrow{\text{heat}}$$

$$C_6H_5\overset{S}{\overset{\|}{C}}NH_2 \;+\; C_6H_5NH_2 \;+\; C_6H_5\overset{S}{\overset{\|}{C}}NHC_6H_5 \;+\; NH_3$$

Thus the reaction between amidines and hydrogen sulfide is analogous to the reaction between amidines and water. *N,N*-Diphenylbenzamidine likewise reacts with hydrogen sulfide at 130°C.

$$2C_6H_5C\!\!\begin{array}{c}\nearrow NH\\[6pt]\searrow N(C_6H_5)_2\end{array} \quad + \quad H_2S \quad\xrightarrow{\text{heat}}$$

$$(C_6H_5)_2NH \;+\; C_6H_5\overset{S}{\overset{\|}{C}}NH_2 \;+\; C_6H_5\overset{S}{\overset{\|}{C}}N(C_6H_5)_2 \;+\; NH_3$$

Amidines can be caused to react with carbon disulfide under the influence of heat (12). *N*-Phenylbenzamidine reacts to form *N*-phenylthiobenzamide and other products; *N*,*N'*-diphenylbenzamidine reacts as follows:
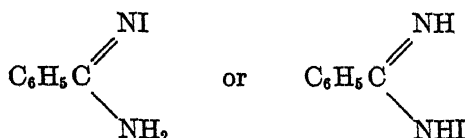
$$C_6H_5C\underset{NHC_6H_5}{\overset{NC_6H_5}{\diagup}} \; + \; CS_2 \; \xrightarrow{\text{heat}} \; C_6H_5\overset{S}{\overset{\|}{C}}NHC_6H_5 \; + \; C_6H_5NCS$$

21. Reaction with halogens

In 1893 Beckmann and Fellrath (9) reported that *N*-methyl-*N*-phenyl-*N'*-benzylbenzamidine ($C_{21}H_{20}N_2$) reacted with bromine. The color of the bromine disappeared as it was added to a chloroform solution of the amidine, and a heat of reaction was noticed. The product was colorless after crystallization from ethanol and had the empirical formula of $C_{21}H_{20}N_2Br_2$. The authors reported that the compound acted like a hydrobromide ($C_{21}H_{19}N_2Br \cdot HBr$), and that oxidation with dilute potassium permanganate produced bromine-free products: benzoic acid, benzylamine, and methylaniline. Beckmann and Fellrath did not attempt to draw any conclusions from the results, but thought that one bromine atom had replaced a hydrogen in a side chain.

Dains and Griffin (36) observed that *N*,*N'*-diphenylformamidine could absorb bromine to form a yellow addition product. This product could be hydrolyzed with dilute potassium hydroxide to yield aniline, *p*-bromoaniline, and *p*-bromoformanilide. These authors also made no attempt to draw any conclusions from the experiments.

Bougault and Robin (16) in 1920 reported that benzamidine hydrochloride reacts with an iodine–potassium iodide solution in the presence of sodium hydroxide to form an iodoamidine, a pale yellow solid. The authors suggest that this reaction may be useful in the identification of amidines, since the product is stable in the air. The following formulas were proposed for *N*-iodobenzamidine:

$$C_6H_5C\underset{NH_2}{\overset{NI}{\diagup}} \qquad \text{or} \qquad C_6H_5C\underset{NHI}{\overset{NH}{\diagup}}$$
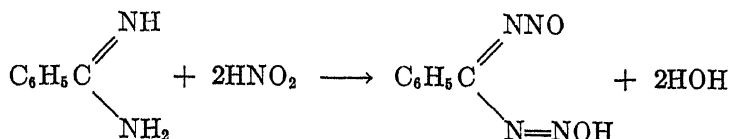
In 1923 Robin (139) further reported that a sodium hypochlorite solution could be used as well, producing a white chloroamidine immediately. Various aromatic amidines were used in like experiments. An excess of cold sodium hydroxide solution or an acidic potassium iodide solution regenerates the amidine.
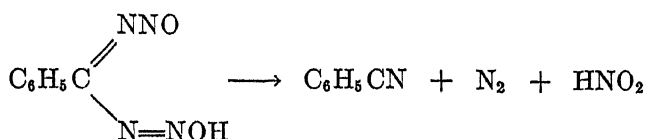
22. Effect of nitrous acid

Since unsubstituted amidines are strong bases, one might expect the amino group to react similarly to that in primary amines. Lossen, Mierau, Kobbert, and Grabowski (89, 90) have studied the action of nitrous acid on amidines and the results indicate that the analogy cannot be extended very far.

When an aqueous solution of benzamidine hydrochloride and an equimolecular amount of sodium nitrite is concentrated to dryness, the nitrite salt is formed along with benzonitrile and benzamide.

When the hydrochloride of benzamidine is treated with an excess of sodium nitrite and hydrochloric acid, there is formed a dinitroso derivative which possesses both acid and basic properties.
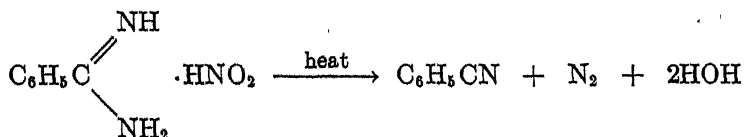
$$C_6H_5C\underset{NH_2}{\overset{NH}{\Big<}} + 2HNO_2 \longrightarrow C_6H_5C\underset{N=NOH}{\overset{NNO}{\Big<}} + 2HOH$$

In general, these amphoteric derivatives decomposed very easily as follows:

$$C_6H_5C\underset{N=NOH}{\overset{NNO}{\Big<}} \longrightarrow C_6H_5CN + N_2 + HNO_2$$
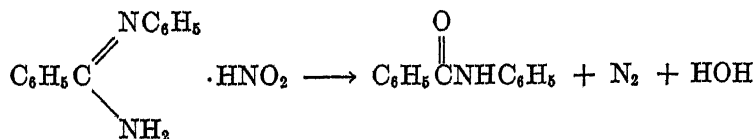
The dioxytetrazotic acids could not be prepared successfully in the free state, but the acid or basic salts could be isolated and analyzed since they proved to be more stable. The dry metallic salts decomposed with explosive violence. The formation of the dioxytetrazotic acids is characteristic only of the unsubstituted amidines.

Nitrite salts of amidines are sufficiently stable to be isolated. The hydrochloride and a silver nitrite solution are allowed to react and the solvent removed at 30–40°C. after separation of the silver chloride. Benzamidine nitrite decomposes upon heating to form benzonitrile.
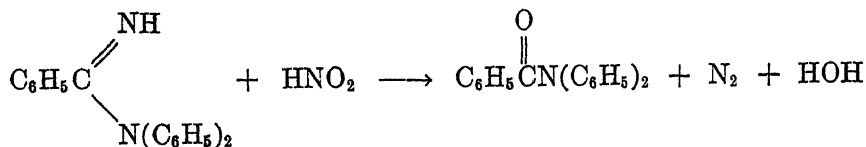
$$C_6H_5C\underset{NH_2}{\overset{NH}{\Big<}} \cdot HNO_2 \xrightarrow{\text{heat}} C_6H_5CN + N_2 + 2HOH$$

The nitrite of N-ethylbenzamidine can be formed from the hydrochloride and silver nitrite; this nitrite can be crystallized from ethanol and ether, but an attempt to use water resulted in decomposition. The heating of an aqueous solution of N-phenylbenzamidine nitrite produced the following decomposition.
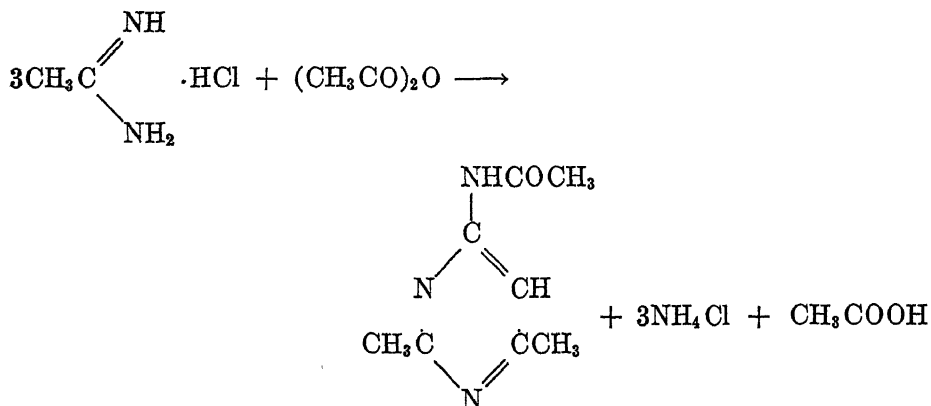
$$C_6H_5C\underset{NH_2}{\overset{NC_6H_5}{\Big<}} \cdot HNO_2 \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}NHC_6H_5 + N_2 + HOH$$

Lossen et al. (90) also report that N,N'-diphenylbenzamidine is not changed by the action of nitrous acid and that the nitrite salt could not be formed. All attempts to prepare the nitrite of N,N-diphenylbenzamidine resulted in the formation of diphenylbenzamide.

$$C_6H_5C\begin{matrix}\nearrow NH \\ \searrow N(C_6H_5)_2 \end{matrix} + HNO_2 \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}N(C_6H_5)_2 + N_2 + HOH$$
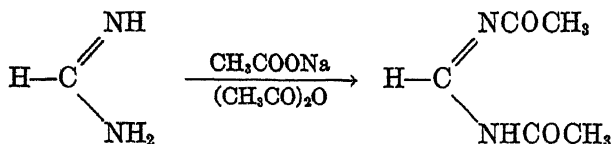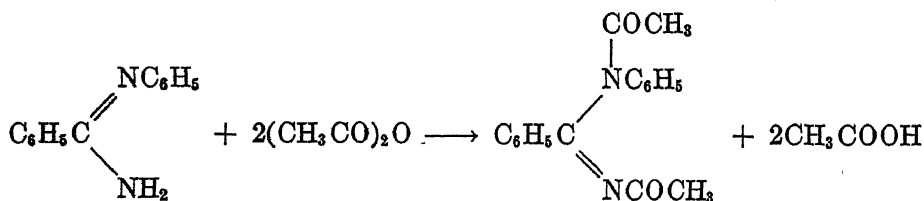
23. Action of acetic anhydride

According to Pinner (109) aliphatic unsubstituted amidines decompose when heated in the presence of acetic anhydride to form dialkylaminopyrimidines. Thus, acetamidine hydrochloride forms 2,4-dimethyl-6-acetylaminopyrimidine when heated with sodium acetate and acetic anhydride at 185°C. (115).

$$3CH_3C\begin{matrix}\nearrow NH \\ \searrow NH_2 \end{matrix}\cdot HCl + (CH_3CO)_2O \longrightarrow$$

$$+ 3NH_4Cl + CH_3COOH$$

Aromatic unsubstituted amidines form triazines under the same conditions. Pinner (112) has reported that formamidine acetate forms a diacetyl derivative when treated with acetic anhydride.
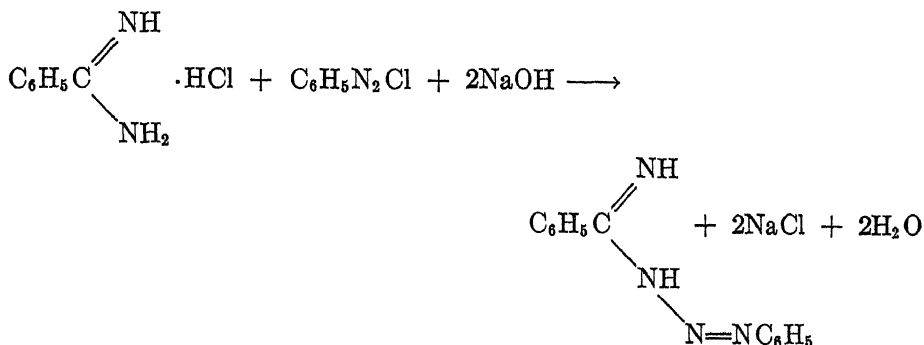
$$H-C\begin{matrix}\nearrow NH \\ \searrow NH_2 \end{matrix} \xrightarrow[(CH_3CO)_2O]{CH_3COONa} H-C\begin{matrix}\nearrow NCOCH_3 \\ \searrow NHCOCH_3 \end{matrix}$$

Lottermoser (91) obtained the diacetyl derivative of N-phenylbenzamidine by heating with acetic anhydride.

$$C_6H_5C\begin{matrix}\nearrow NC_6H_5 \\ \searrow NH_2 \end{matrix} + 2(CH_3CO)_2O \longrightarrow C_6H_5C\begin{matrix}\nearrow \overset{\overset{COCH_3}{|}}{N}C_6H_5 \\ \searrow NCOCH_3 \end{matrix} + 2CH_3COOH$$

24. Reaction with diazonium salts

Pinner has reported (109, 115) that benzenediazonium chloride reacts with unsubstituted amidines to form azo derivatives.

$$C_6H_5C\overset{NH}{\underset{NH_2}{\diagdown}} \cdot HCl \ + \ C_6H_5N_2Cl \ + \ 2NaOH \ \longrightarrow$$

$$C_6H_5C\overset{NH}{\underset{NH}{\diagdown}} \ + \ 2NaCl \ + \ 2H_2O$$
$$\underset{N=NC_6H_5}{}$$

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